Selective Transformation of Acyl Fluorides and Chlorides to Nitriles, Arylboronates, and Esters

(フッ化アシルおよび塩化アシルのニトリル、アリールボロン酸エステル、エステルへの選択的な変換反応)

2019.9

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(Doctor's Course)

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Contents

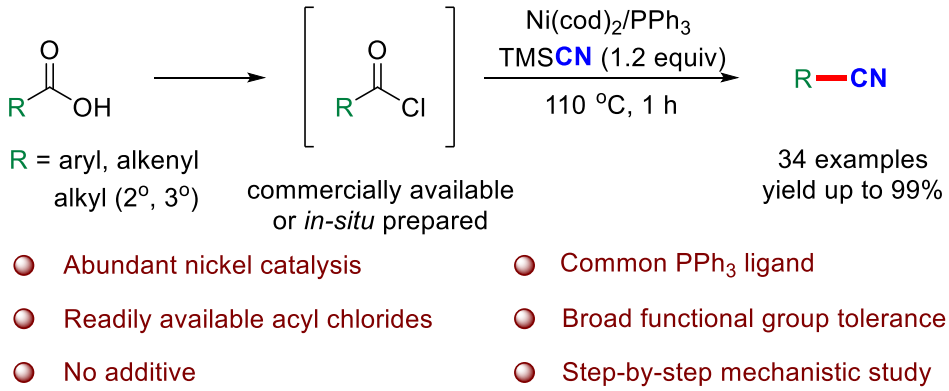
Abstract

Taking into account the growing concerns on the environmental and sustainable events of our society, carboxylic acids and their derivatives as aromatic feedstock alternatives are in high demand. Facile diversifications of carboxylic acids and their derivatives into other valuable adducts offer practical and strategic advantages in the context of complex-molecule synthesis, because they are inexpensive and readily available.

In this PhD Thesis, the Author focuses on the transformations of acyl halides from the readily available carboxylic acids. Cyanation of acyl chlorides were applicable to the synthesis of an array of nitrile compounds bearing a wide range of functional groups under mild and neutral conditions. A series of carboxylic acids can be converted into a wide array of arylboronates via nickel-catalyzed decarbonylative borylation of acyl fluorides. Cyclopentyl methyl ether was firstly designed as a methoxylating agent in methoxylation of acid fluorides, the regiospecific C–OMe bond cleavage avoids the utilization of strong acids or bases. For the successful transformations of acyl halides to nitriles, organoboronates and esters realized the utilization of carboxylic acids as aromatic electrophiles. This PhD Thesis provides new strategies to convert the earth-abundant carboxylic acids into the valuable adducts via in-situ or isolated acyl halides, which could be versatile coupling partners for further transformations.

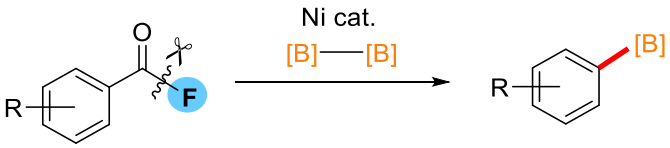
Chapter 2. Nickel-Catalyzed Decarbonylative Cyanation of Acyl Chlorides

As the continuous research interests in transformation of acyl halides, a more efficient synthetic protocol for nitriles was studied in this Chapter. This newly developed Ni-catalyzed decarbonylative cyanation of acyl chlorides with trimethylsilyl cyanide (TMSCN) is applicable to structurally diverse (hetero)aryl, alkenyl, and alkyl nitriles as well as bioactive molecules in high efficiency, which rendered it a powerful and practical protocol to synthesize an array of organonitriles bearing a wide range of functional groups under mild and neutral conditions. The step-by-step experimental studies revealed that the reaction sequences of the present catalytic reaction are oxidative addition, transmetalation, decarbonylation, and reductive elimination.



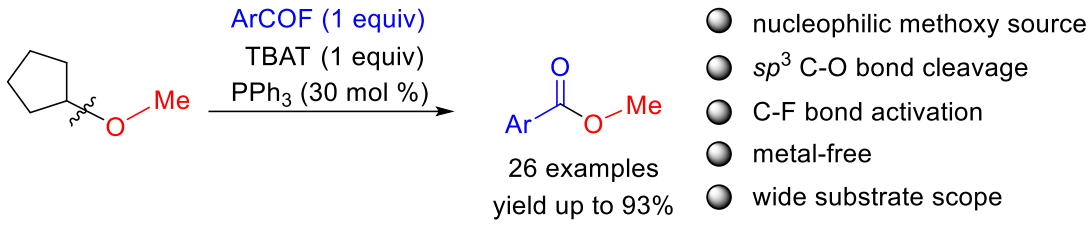
Chapter 3. Nickel-Catalyzed Decarbonylative Borylation of Acyl Fluorides

Acyl fluorides are one of the carboxylic acid derivatives, displaying a great stability, high reactivity, and can be versatile building blocks as acyl, aryl, and F sources with their unique intrinsic nature. However, the related reports is quite rare. In this Chapter, the Author successfully demonstrated the $Ni(cod)_2/PPh_3$ catalyst system for decarbonylative borylation of acyl fluorides with bis(pinacolato)diboron, in which acyl fluorides served as aryl sources. The easy access of the starting acyl fluorides indicates that these results might become an alternative to the existing decarbonylation events.



Chapter 4. PPh_3-Assisted Esterification of Acyl Fluorides with Ethers via $C(sp^3)$–O Bond Cleavage Accelerated by TBAT

In this Chapter, the Author describes methoxylation of acyl fluorides with cyclopentyl methyl ether (CPME) mediated by tetrabutylammonium difluorotriphenysilicate (TBAT) via regiospecific C–OMe bond cleavage in the presence of a catalytic amount of PPh_3. Eco-friendly and easily available CPME is utilized not only as the solvent, but a methoxylating agent in this transformation. The present method is featured by C–O and C–F bond cleavage under metal-free conditions, good functional-group tolerance, and wide substrate scope. Mechanistic studies revealed that the radical process is not involved.


ArCOF (1 equiv)
TBAT (1 equiv)
PPh3 (30 mol %)
Me
O
Ar
O
O
Me
26 examples
yield up to 93%
nucleophilic methoxy source
sp3 C-O bond cleavage
C-F bond activation
metal-free
wide substrate scope

CHAPTER 1

General Introduction

1-1 Introduction

Carboxylic acids and their derivatives have drawn much attention during past decades, because of their natural abundance and easy availability, which has further increased recent advances in carboxylation reactions.[1] Besides, a carboxy group is a fundamental functional group often found in a broad range of organic molecules, including natural products, pharmaceuticals, agrochemicals, and functional materials. Further transformations of carboxylic acids and their derivatives to versatile compounds are also attracting a considerable interest,[2] especially via acyl halides.

Because acyl halides are arguably as the simplest and most atom-economical carboxylic acid derivatives, display many superiorities than the corresponding carboxylic derivatives such as phenolic esters, benzamides, aromatic thioesters, and acid anhydrides. They show higher reactivity than other acid series and easier preparation from the corresponding carboxylic acids. In addition, they could serve as versatile building blocks such as acyl, aryl as well as halide sources (Figure 1-1).

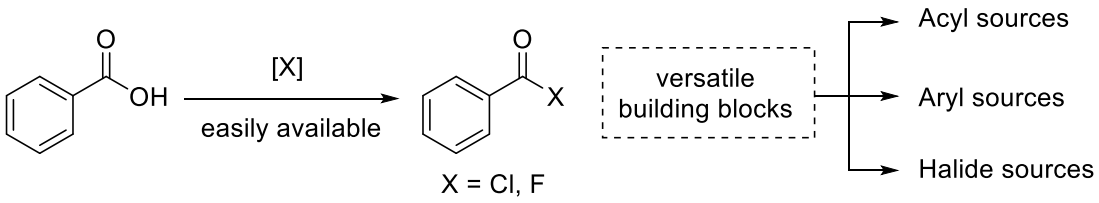


Figure 1-1

Although the utilization of acyl halides in various transformations have been impressively developed and well established, development of new transformations of acyl halides have still drawn much attention. In particular, efficient conversions of acyl chlorides to valuable building blocks under milder conditions are highly demanded. Besides, the comparation of acyl chlorides with acyl fluorides in transition-metal-catalyzed cross-coupling reactions are of interest.

1-2 Transformations of Acyl Chlorides

There are three representative types of transformations of acyl chlorides.

(1) Utilization of acyl chlorides as an acyl source.

(2) Utilization of aryl chlorides as an acyl source.

(3) Utilization of acyl chlorides as an halide source.

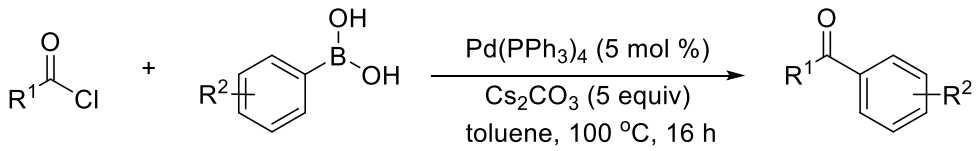
1-2-1 Utilization of Acyl Chlorides as Acyl Sources

In the past decades, acyl chlorides mainly served as an acyl source in transition-metal-catalyzed or TM-free couplings with organometallic reagents or unsaturated compounds to give various ketones. Although these protocols have been frequently used to synthesize various ketones, there are still some limitations.

1-2-1-1 Coupling with Organoboron Reagents

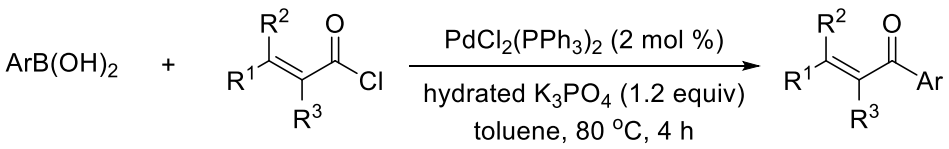
In 1999, Haddach and McCarthy firstly reported $Pd(PPh_3)_4$-catalyzed Suzuki-Miyaura reaction of acyl chlorides and arylboronic acids in the presence of Cs_2CO_3 under anhydrous conditions. Regardless of steric and electronic effects, aromatic and aliphatic acyl chlorides could react with (hetero)arylboronic acids, which provided a new method for the synthesis of ketones in moderate to good yields (Scheme 1-1).[3]

Scheme1-1



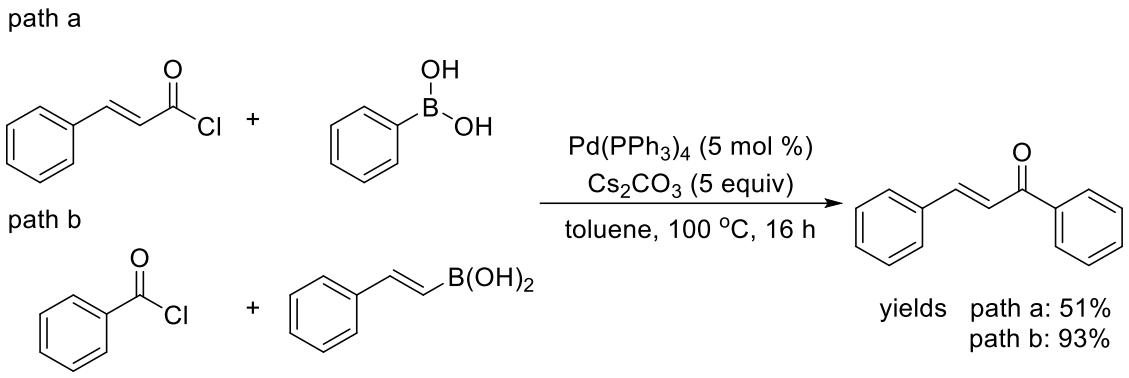
Except for aromatic and aliphatic acyl chlorides, commercially available or easily prepared *α,β*-unsaturated acyl chlorides were also applied in palladium-catalyzed Suzuki-Miyaura-type coupling reactions. In 2003, Ogura *et al*. developed a convenient method for preparing aromatic *α,β*-unsaturated ketones from the reactions of *α,β*-unsaturated acyl chlorides with arylboronic acids or the corresponding boroxines. Notably, hydrated K_3PO_4 played a significant role in the catalytic system (Scheme 1-2).[4]

Scheme 1-2



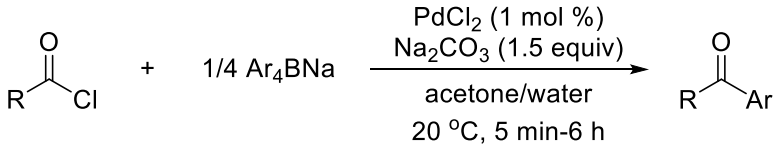
Rolando *et al.* found that couplings of cinnamoyl chloride with various phenylboronic acids and couplings of benzoyl chloride with phenylvinylboronic acid could give comparable results under the identical reaction conditions. Particularly, substituents on the acyl chlorides or boronic acids did not affect the efficiency of this reaction, which provided a general method for the synthesis of chalcones (Scheme 1-3).[5]

Scheme 1-3



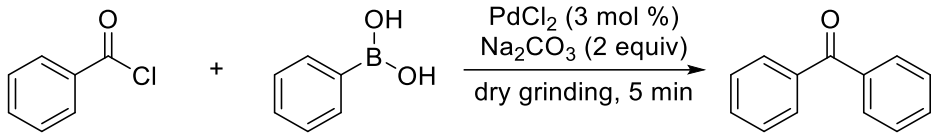
Korolev and Bumagin developed carbonyl retentive couplings of stable sodium tetraarylborates with acyl chlorides to synthesize unsymmetrical aromatic ketones in high yields. The high catalytic activity of palladium salts in aqueous organic media made the method economically attractive. Mild optimized conditions allowed functionalized substrates well tolerated in this reaction (Scheme 1-4).[6]

Scheme 1-4



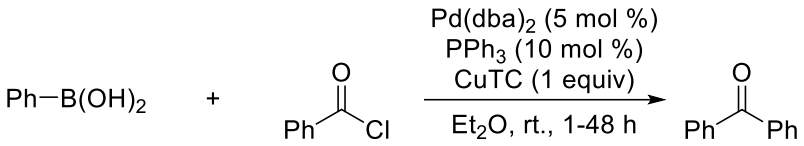
Pd-catalyzed cross-coupling reactions of boronic acids with acyl chlorides for aromatic ketone synthesis in the presence of Na_2CO_3 at room temperature were described by Bandgar and Patil. Ligand- and solvent-free conditions, highly rapid reaction rate and good to excellent yields are important features of this method (Scheme 1-5).[7]

Scheme 1-5



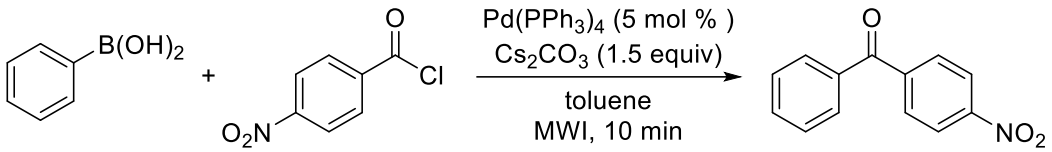
Nishihara *et al*. found that palladium-catalyzed and copper(I)-mediated coupling reactions of acyl chlorides with boronic acids could proceed smoothly under neutral conditions. Besides, a wide range of substrates bearing an electron-donating or electron-withdrawing substituent on the aromatic ring were compatible (Scheme 1-6).[8]

Scheme 1-6



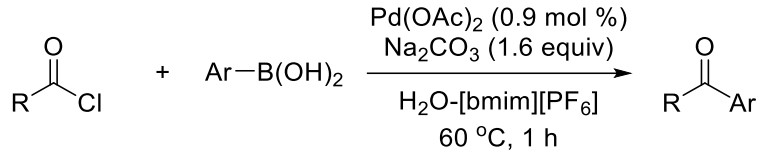
Microwave irradiation-promoted cross-coupling of acyl chlorides with arylboronic acids provided a convenient method for preparation of aromatic ketones. Mild reaction conditions afforded symmetrical and unsymmetrical aryl ketones in reasonable to high yields within a short time (Scheme 1-7).[9]

Scheme 1-7



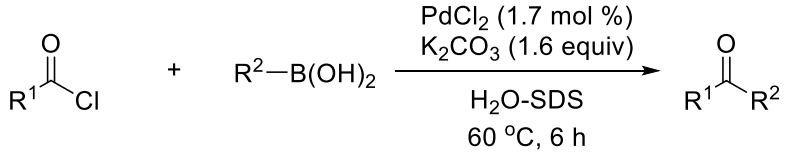
Employment of less toxic, environmentally compatible reagents have attracted much attention in green chemistry, especially conducting reaction in water. In 2006, Zhang *et al*. reported palladium acetate-catalyzed smooth coupling reactions of arylboronic acids with acyl chlorides in water in the presence of 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), giving high yields of ketones without phosphine ligands.[10] The $Pd(OAc)_2$-H_2O-[bmim][PF_6] catalytic system was air-stable, insensitive to moisture, good solubility for organic substrates, and reusable for 8 times with high efficiency (Scheme 1-8).

Scheme 1-8



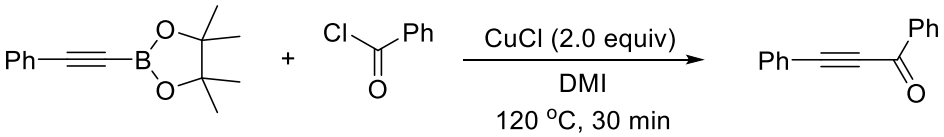
The sodium dodecyl sulfate (SDS)-promoted cross-coupling reactions of arylboronic acids with acyl chlorides in water were developed by Cheng and co-workers, in which a variety of aryl ketones were obtained under mild conditions in good yields without the use of phosphine ligands in an atmospheric air (Scheme 1-9).[11]

Scheme 1-9



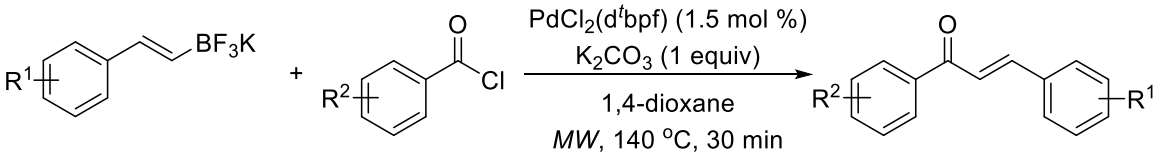
Alkynylboronate can be employed as a practical and versatile precursor for a variety of π-conjugated organic compounds. In the presence of a stoichiometric Cu(I) salt, cross-coupling reactions of acyl chlorides with alkynylboronates gave rise to the corresponding conjugated ynones in DMI under neutral conditions (Scheme 1-10).[12]

Scheme 1-10



Potassium styryltrifluoroborates were also proved to be good coupling partners in the $PdCl_2(d^tbpf)$-catalyzed reaction of acyl chlorides, furnishing α,β-unsaturated aromatic ketones or chalcones in a single step process under microwave heating (Scheme 1-11).[13]

Scheme 1-11

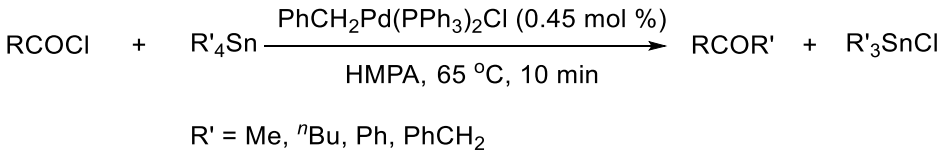


As examples shown above, Pd-catalyzed cross-coupling of acyl chlorides with organoboron compounds are frequently used for the synthesis of ketones. However, decarbonylative Suzuki-Miyaura reactions of acyl chlorides to biaryls still remain unexplored.

1-2-1-2 Coupling with Organotin Reagents

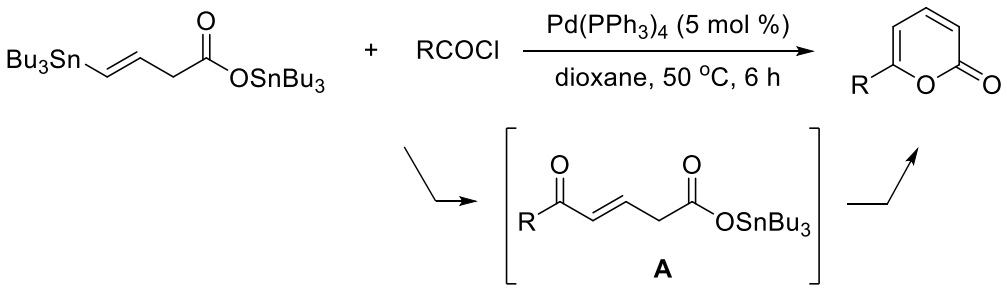
In 1978, Stille firstly found that organotin compounds readily underwent palladium-catalyzed coupling with acyl chlorides (Scheme 1-12). [14] This method was highlighted by the following advantages; quantitative yields in many cases, a wide range of functional groups including NO_2, CN, Cl, Br, OMe, CHO as well as methyl ester, air atmosphere; clean reaction with simple work-up, short reaction time within 15 min, easily confirmation of reaction completion by yellow solution turning to black, highly catalytic turnover numbers of 20,000.

Scheme 1-12



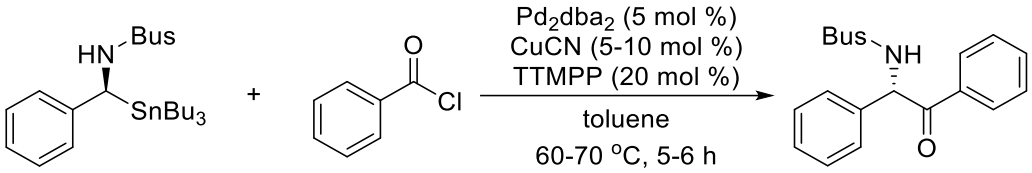
Stereoselective annulation of functional vinylstannanes with acyl chlorides catalyzed by palladium was developed by Parrain and Duchêne (Scheme 1-13),[15] which probably proceeded through Stille reaction/cyclization sequence for biological active α-pyran-2-ones synthesis. The proposed mechanism demonstrated that an initial step was the formation of 5-substituted 5-oxopent-3-enoate **A** by a classical pathway of Stille reaction mechanism: oxidative addition, transmetalation, and reductive elimination. Then, target products were obtained by a laconization reaction of compound **A**.

Scheme 1-13



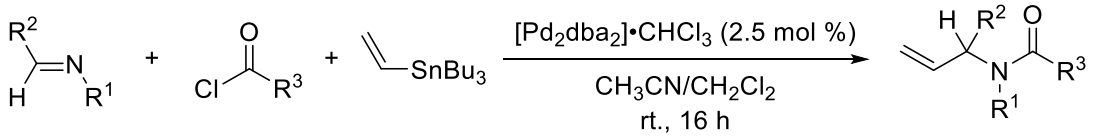
Stille-type coupling of stannyl sulfonamide with benzoyl chloride was studied by Kells and Chong, in which expected ketones were obtained in high yields with inversion of stereochemistry at the benzylic carbon (Scheme 1-14). [16] Tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) are the most efficient ligand in the present reactions, probably because the highly basic and bulky ligand TTMPP could suppress competitive *β*-hydride elimination.

Scheme 1-14



As well known, imines are not suitable cross-coupling partners under palladium catalysis due to a nitrogen anion or a palladium cation in the formed Pd–C complex is unstable. Therefore, a strategy to neutralize the nitrogen anionic charge was postulated by adding acyl chlorides to form *N*-acyl iminium, which could be chelated with palladium(0) species. With this idea in mind, palladium-catalyzed three-component Stille-type coupling of imines, acyl chlorides, and organotin reagents was studied by Arndtsen and co-workers for *α*-substituted amides and *N*-protected amines synthesis. Mechanistically, this process provided an oxidative addition/reductive elimination-based alternative to nucleophilic approaches for C–C bond formation with imines (Scheme 1-15). [17]

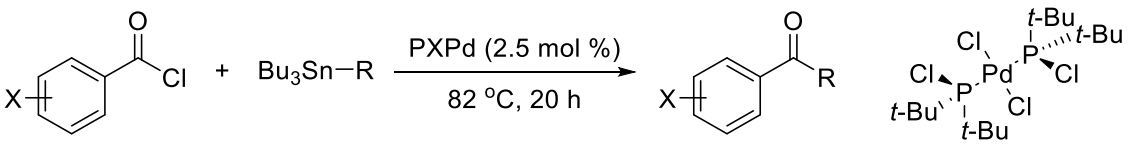
Scheme 1-15



Wolf *et al.* reported bis-(di-*tert*-butylchlorophosphine)palladium(II) dichloride-catalyzed cross-coupling of acyl chlorides with organostannanes in refluxing acetonitrile, providing means to prepare aliphatic and aromatic ketones in good to high yields (Scheme 1-16). [18] Although bromide and iodide are known to be reactive for oxidative addition to palladium catalysts, they were compatible in this reaction. The

choice of di-*tert*-butylchlorophosphine was crucial to the chemoselective activation of halobenzoyl chlorides by its less electron-donating ability.

Scheme 1-16



X = -Cl, -Br, -CN, -Me, -OMe, -OCH_2O-
R = alkynyl, Ph, 2-furyl, 2-thienyl

PXPd

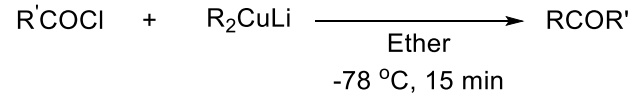
1-2-1-3 Coupling with Other Organometallic Reagents

Besides the couplings of acyl chlorides with organoboron and organotin compounds, the reaction of acyl chlorides with other organometallic reagents such as organocopper, -manganese, -silicon, -zinc, -magnesium, -aluminum, -silver, -bismuth, and -lithium reagents were also introduced in this Chapter.

(1) Coupling with Copper Reagents

Whitte reported that lithium dimethyl- and di-*n*-alkyl copper reagents reacted cleanly with alkyl carboxylic acid chlorides under extremely mild conditions, forming the corresponding methyl and *E*-alkyl ketones in good to excellent yields (Scheme 1-17).[19] In terms of acyl chlorides, only electron-withdrawing groups substituted benzoyl chlorides were investigated, affording moderate yields of the corresponding ketones.

Scheme 1-17

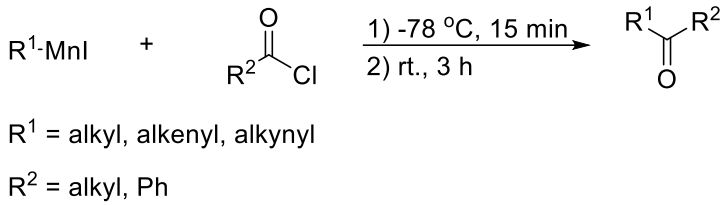


R' = aryl, alkyl R = Me, Et, Bu

(2) Coupling with Manganese Reagents

Normant reported the reaction of alkylmanganese(II) iodides with primary, secondary, or tertiary acyl chlorides, leading to the corresponding ketones in moderate to good yields. An advantage of this method was that alkylmanganese(II) iodide is stable at room temperature (Scheme 1-18).[20]

Scheme 1-18



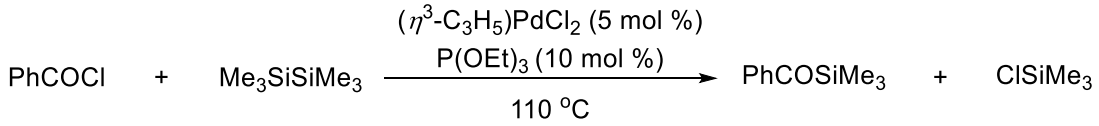
R^1 = alkyl, alkenyl, alkynyl

R^2 = alkyl, Ph

(3) Coupling with Organosilicon Reagents

In 1980, Yamamoto *et al*. demonstrated that palladium(II) complex with $P(OEt)_3$ catalyzed the coupling reactions of acyl chlorides and hexamethyldisilane to provide a direct preparative route to benzoyltrimethylsilane without a CO loss. The generality of this transformation revealed that an electronic nature of acyl chlorides affected the carbonyl retention, for example, benzoyl chloride bearing strong electron-withdrawing groups such as NO_2 cannot be compatible, affording a mixture of acylsilane and arylsilane in 37% and 28% yields, respectively (Scheme 1-19).[21]

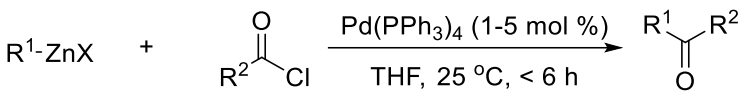
Scheme 1-19



(4) Coupling with Zinc Reagents

Negishi *et al*. found organozinc reagent also could participate in Pd-catalyzed acylation of acyl chlorides, ketones were obtained in good to excellent yields (Scheme 1-20).[22] The addition of the palladium catalyst dramatically increased the yields of the target products, less than 10% corresponding ketones were formed without the palladium catalyst.

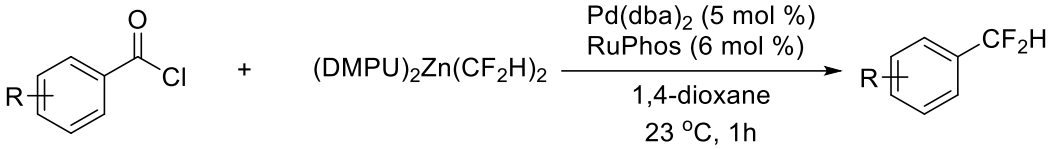
Scheme 1-20



In 2018, Ritter and co-workers found palladium-catalyzed decarbonylative difluoromethylation reaction of acyl chlorides with $(DMPU)_2Zn$-$(CF_2H)_2$ to afford

difluoromethyl arenes at room temperature. Their study not only provided a new aromatic difluoromethylation method, but also gave new insights into the decarbonylative step at room temperature (Scheme 1-21).[23] Mechanistic studies demonstrated the oxidative adduct prepared from $Pd(dba)_2$, RuPhos, and acyl chloride cannot proceed decarbonylation progress, however, smooth decarbonylation of oxidative adduct was observed in the presence of zinc reagent, which further proved the importance of zinc reagent introduction in this transformation.

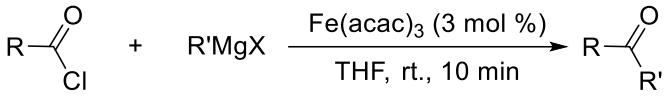
Scheme 1-21



(5) Coupling with Grignard Reagent

Marchese *et al*. reported $Fe(acac)_3$-catalyzed coupling reaction of acyl chlorides with Grignard reagents at room temperature. However, Grignard reagents are also limited by their poor tolerance of functional groups due to their highly activity (Scheme 1-22).[24]

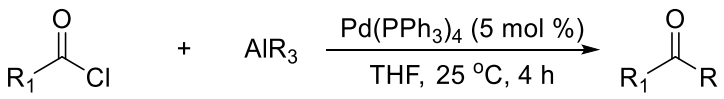
Scheme 1-22



(6) Coupling with Aluminum Reagents

Apart from other organometallic reagents, the formation of ketones from acyl chlorides with trialkylaluminum is pretty difficult, due to the fast side reaction of trialkylaluminum with the resulting ketones forming the corresponding alcohols. In order to solve this problem, treatment of acyl chlorides with trialkylaluminum in the presence of catalytic amount of a palladium catalyst was examined, which showed prior results than other transition metal catalysts, such as rhodium, nickel, and ruthenium (Scheme 1-23).[25]

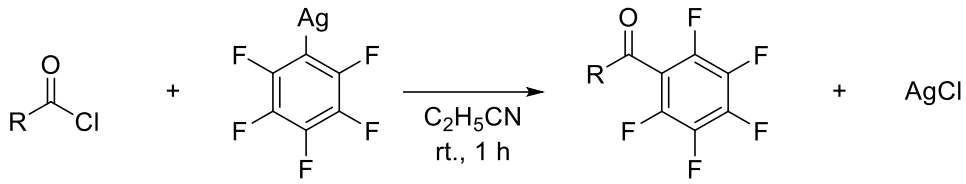
Scheme 1-23



(7) Coupling with Silver Reagents

A mild and general method for pentafluorobenzophenone synthesis was reported by Tyrra *et al* by introducing a pentafluorophenyl group into an acyl fragment, in which acyl chlorides and convenient accessible pentafluorophenylsilver were utilized in this reaction. Ten selected examples of pentafluorobenzophenones were obtained at room temperature for 1 h (Scheme 1-24).[26]

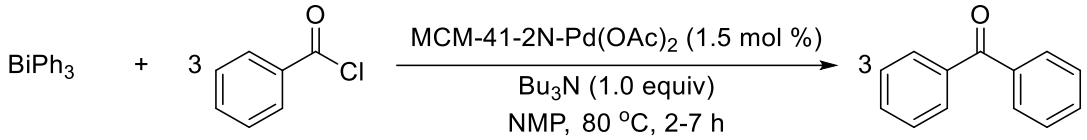
Scheme 1-24



(8) Coupling with Bismuth Reagents

Cai and co-workers achieved the first phosphine-free, heterogeneous, atom-efficient cross-coupling reaction of triarylbismuths and acyl chlorides in *N*-methylpyrrolidone with Bu_3N as the base at 80 °C in the presence of 1.5 mol-% MCM-41-immobilized bidentate nitrogen palladium complex [MCM-41–2N-Pd$(OAc)_2$, MCM = mobile crystalline material] to yield a variety of unsymmetrical biaryl ketones in good to excellent yields (Scheme 1-25).[27]

Scheme 1-25

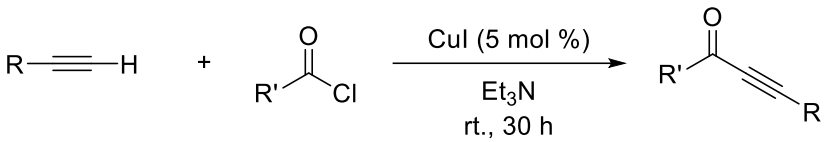


1-2-1-4 Coupling with Alkynes

Sonogashira-Hagihara-type reactions of acyl chlorides with alkynes to alkynone were well documented under palladium and copper catalysis in a carbonyl retentive manner. However, the arynes synthesis from decarbonylative Sonogashira-Hagihara reactions of acyl chlorides are still unexplored. In 1999, Kundu reported copper(I) iodide-catalyzed acylation of acyl chlorides with terminal alkynes in triethylamine at room temperature for 30 h (Scheme 1-26).[28] This method is featured by compatibility of a series of alkyl and

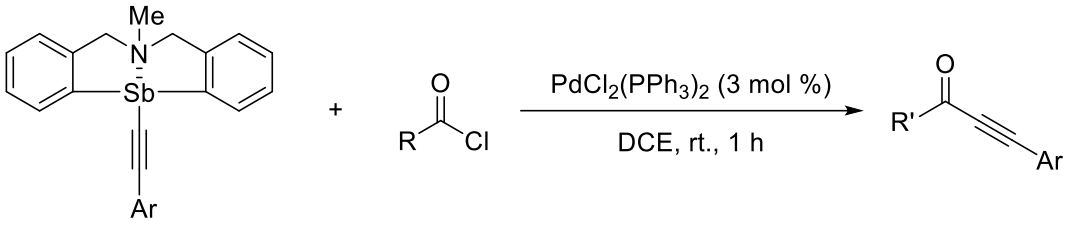
(hetero)aryl alkynes with acyl chlorides in the absence of the palladium catalyst. However, primary alky acyl chlorides could not succeed in this reaction. In addition, a large amount of triethylamine was used as the base as well as the solvent.

Scheme 1-26



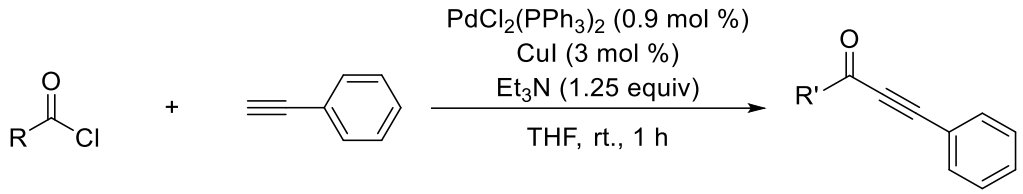
Palladium-catalyzed, copper-, base-free Sonogashira-Hagihara-type coupling of acyl chlorides with ethynyl-1,5-azastibocines as the Sb reagents was developed by Kurita and co-workers, in which ethynyl-1,5-azastibocines were employed as the key starting compounds instead of terminal alkynes to shorten the reaction time, to improve the efficiency and, to avoid the exogenous base (Scheme 1-27).[29] Single-crystal X-ray analysis of the ethynyl-1,5-azastibocine showed the presence of intramolecular Sb···N interaction which is responsible for the remarkable reactivity enhancement of the 1,5-azastibocines in the present reaction. However, the pre-synthesis of the Sb reagents limited their utilization in *α,β*-acetylenic ketones synthesis.

Scheme 1-27



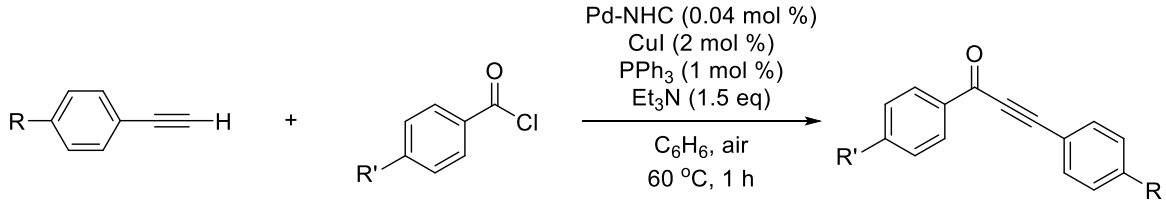
In 2005, Cox developed a facile, high-yielding coupling of acyl chlorides with terminal alkynes catalyzed by the combination of palladium and copper catalysts in the presence of Et_3N. Terminal alkynes bearing alkyl, ester, silyl, silyoxy, and protected amino groups were well tolerated. In terms of acyl chlorides, aryl, primary, and tertiary acyl chlorides were subjected in the present transformation, which provided a convenient one-pot route to acetylenic ketones (Scheme 1-28).[30]

Scheme 1-28



A remarkable improvement was achieved by Vasilyev and co-workers, they could reduce the palladium loading as low as 0.04 mol %. Besides, the palladium(II) acyclic diaminocarbene complexes with high stability in air could afford 1,3-diarylpropynones in 95-98% yields (Scheme 1-29).[31] The selectivity of palladium complexes and electronic effect of the substrates toward cross- and homo-couplings were also investigated.

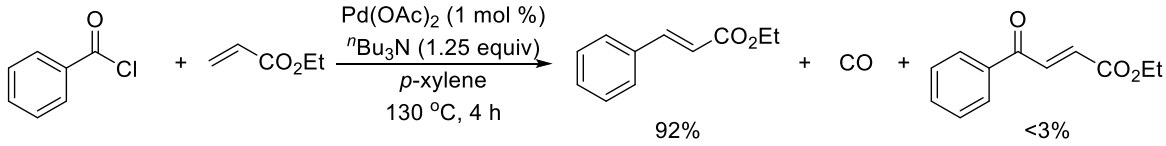
Scheme 1-29



1-2-1-5 Coupling with Alkenes

Mizoroki-Heck-type reactions of acyl chlorides with alkenes via non-decarbonylation and decarbonylation have been reported. In 1982, Blaser and Spencer demonstrated palladium-catalyzed decarbonyltive Mizoroki-Heck-type reactions of acyl chlorides with activated alkenes in the presence of a tertiary amine to give arylated alkenes. The reaction was not sensitive to substituents of acyl chlorides (Scheme 1-30).[32]

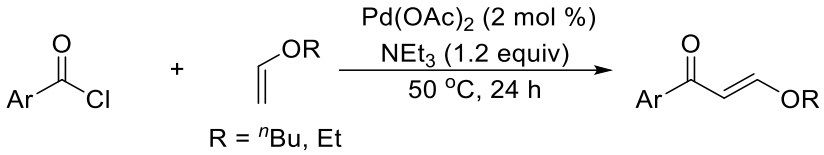
Scheme 1-30



On the contrary, palladium-catalyzed carbonyl retentive Mizoroki-Heck-type reaction of acyl chlorides with alkyl vinyl ethers were reported by Andersson and Hallberg. The reaction tolerated a variety of substituents to give *E*-*β*-aroylated vinyl ethers in moderate

to good yields under mild conditions, although strong electron-withdrawing groups gave inferior yields as a result of a competitive decarbonylative arylation process (Scheme 1-31).[33]

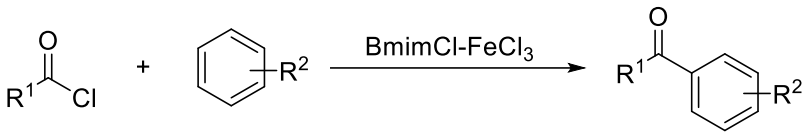
Scheme 1-31



1-2-1-6 Coupling with Arene in Friedel–Craft Reaction

Lewis acid ionic liquid of BmimCl (1-butyl-3-methylimidazolium chloride)–$FeCl_3$ as dual catalyst-solvent were employed in benzophenone and its derivatives synthesis, via Friedel-Crafts acylation of acyl chlorides and benzene derivatives. This environmentally friendly method showed high efficiency, simple isolation procedure, ionic liquids (ILs) reusability (Scheme 1-32).[34]

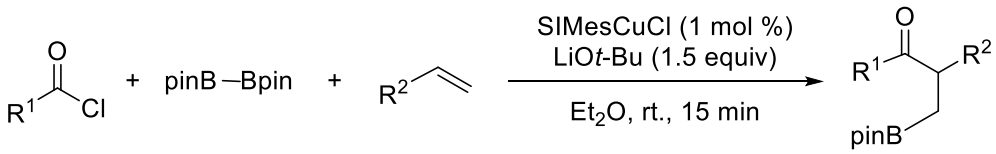
Scheme 1-32



1-2-1-7 Acyl Halides in Addition Reactions

Copper-catalyzed three-component borylation of activated alkenes, acyl chlorides, and diboron was described by Brown in 2017. A wide range of vinyl arenes, 1,3-dienes, and strained bicyclic alkenes well reacted with various acyl chlorides in short reaction time with high efficiency (Scheme 1-33).[35]

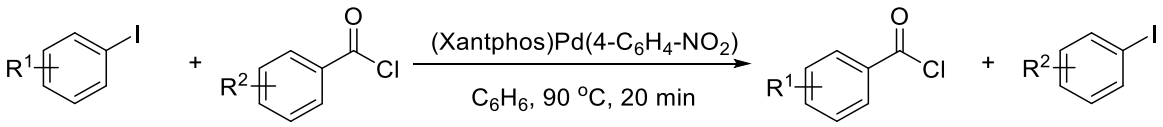
Scheme 1-33



1-2-1-8 Acyl Halides in Acyl Exchange Reactions

Arndtsen *et al*. found that acyl chlorides could undergo metathesis with aryl halides. The method achieved the exchange of σ-bonds by using a palladium catalyst and provided a new idea to synthesize various functionalized aromatic compounds from stable aryl halides (Scheme 1-34).[36]

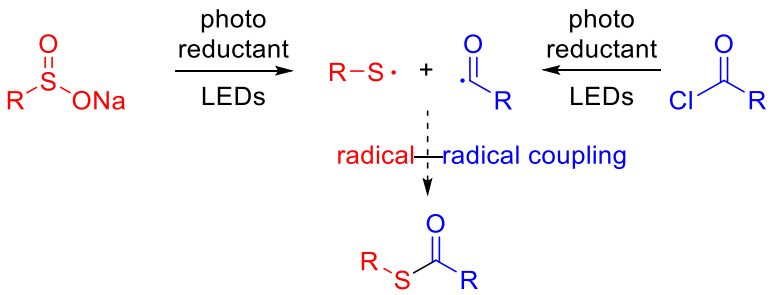
Scheme 1-34



1-2-1-9 Coupling with Sodium Sulfinates

Very recently, Kim and Oh *et al*. developed a visible-light photoredox-catalyzed radical-radical cross-coupling reactions for the synthesis of thioesters, in which acid chlorides and sodium sulfinates were utilized to form acyl and thiyl radicals. This method offered a novel radical-radical coupling strategy to form important synthetic building blocks (Scheme 1-35).[37]

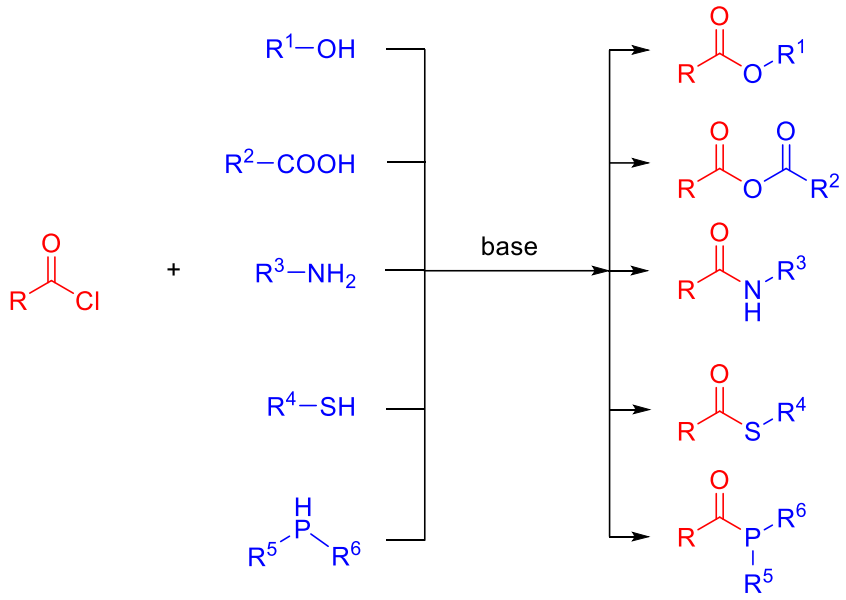
Scheme 1-35



1-2-1-10 Utilization of Acyl Chlorides as an Acyl Source under Transition-Metal Free Conditions

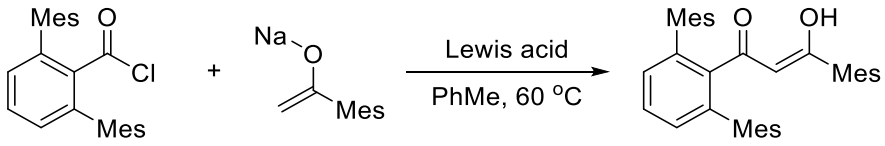
Except transition-metal-catalyzed transformations, acyl chlorides have been frequently used in C−O, C−N, C−S, C−P and C−C bond formation reactions without transition-metal catalyst. For example, acyl chlorides could smoothly react with phenol/alcohol, carboxylic acid, aniline, thiol, and phosphine in the presence of suitable bases to provide the corresponding phenol esters,[38] anhydride,[39] benzamine,[40] thioester[41] and acyl phosphine[42] (Scheme 1-36).

Scheme 1-36



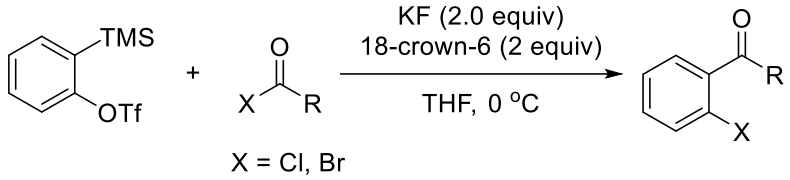
Acyl chlorides could also participate in the C−C bond formation reactions. Marshak *et al*. revealed that acid chlorides were more effective electrophiles than the corresponding esters in congested steric regimes. The Lewis acid-mediated condensation of acid chlorides with enolates provided a new strategy to synthesize the sterically hindered *β*-diketones (Scheme 1-37).[43]

Scheme 1-37



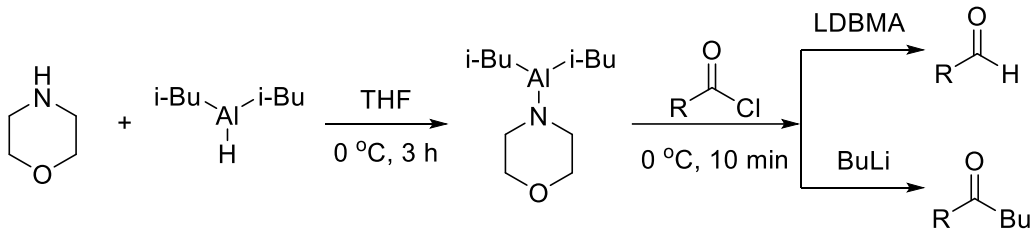
The utilization of acyl chlorides in transition-metal-free C−C bond construction via aryne intermediates was developed by Yoshida and Kunai. The acyl moieties and halogens from acyl chlorides and bromides could be simultaneously introduced to arynes to form *ortho*-halogenated ketones (Scheme 1-38).[44]

Scheme 1-38



An *et al*. reported a facile, alternative, and one-pot protocol for the synthesis of aldehydes and ketones from their respective acid chlorides. The reaction of Morpholine amide intermediates with acyl chlorides in the presence of lithium diisobutylmethoxy aluminum hydride (LDBMA) or organolithium reagents afforded aldehydes or ketones in excellent yields. This method featured high yields (almost up to 95%), mild reaction conditions, low costs, and process simplicity (Scheme 1-39).[45]

Scheme 1-39



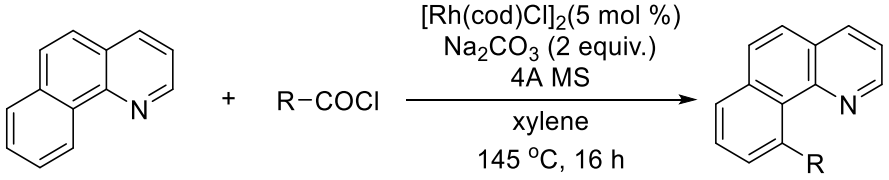
1-2-2 Utilization of Acyl Chlorides as Aryl Sources

The utilization of acyl chlorides is not limited to an acyl source, but an aryl source.

1-2-2-1 Coupling with Arenes

Zhao and Yu developed an efficient regioselective functionalization of aromatic C–H bonds using acyl chlorides as the coupling partners. This Rh(I)-catalyzed decarbonylative (*N*-hetero)aromatic C–H arylation reaction proceeded under ligand-free conditions (Scheme 1-40).[46]

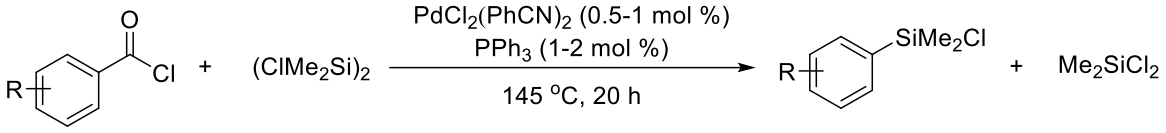
Scheme1-40



1-2-2-2 Coupling with organosilicon

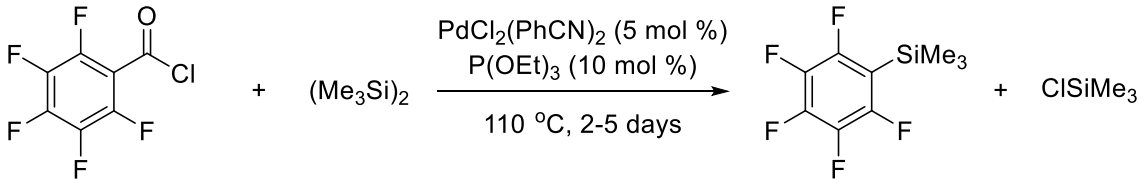
A new synthetic procedure aimed for the preparation of arylsilane were reported by Rich. Same phenomenon was observed in the palladium-catalyzed reaction of strong electron-withdrawing group-substituted acyl chlorides with hexamethyldisilane, a mixture of acylsilane and arylsilane was obtained. When methylchlorodisilanes were utilized instead of disilane, good selectivity was detected without any acylsilane formation, which suggested the vital effect of silicon substitution in this reaction. In addition, the silylative decarbonylation process can selectively proceed with low metal catalyst loading (500-1000 ppm Pd) under solvent-free conditions (Scheme 1-41).[47]

Scheme 1-41



Kashiwabara and Tanaka reported palladium-phosphite complexes selectively catalyzed decarbonylative silylation of pentafluorobenzoyl chloride with hexamethyldisilane to form pentafluorophenytrimethylsilane as the sole product (Scheme 1-42).[48] Mechanistic study showed that decarbonylation progress was very rapid even at room temperature, proved by the selective formation of *trans*-$C_6F_5PdCl(PPh_3)_2$ by mixing pentafluorobenzoyl chloride with $Pd(PPh_3)_4$. In addition, 4-fluorobenzoyl chloride and 3,5-difluorobenzoyl chloride were also examined, furnishing the mixture of acylsilane and arylsilane, which suggested a pentafluorophenyl group was the key to facilitate the decarbonylation step.

Scheme 1-42

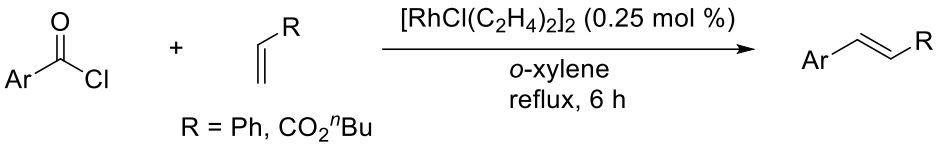


1-2-2-3 Coupling with Alkenes

Miura *et al*. developed rhodium-catalyzed Mizoroki-Heck-type arylation of alkenes

with acyl chlorides under ligand- and base-free conditions. The reaction was highlighted by its high efficiency and simple work-up procedure; only filtration, evaporation, and washing with methanol, then the desired products were obtained by second filtration. Notably, a simple styrene was also a good coupling partner in this transformation, which provided a new convenient route to vinyl-substituted aromatic compounds (Scheme 1-43).[49]

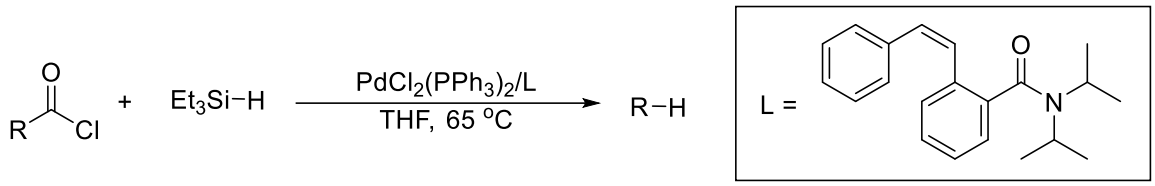
Scheme 1-43



1-2-2-4 Acyl Chlorides in Decarbonylative Reductions

Palladium-catalyzed selective reduction of acyl chlorides was reported by Xu *et al.*, in which an employed amide-derived olefin ligand is the key for this transformation (Scheme 1-44).[50]

Scheme 1-44



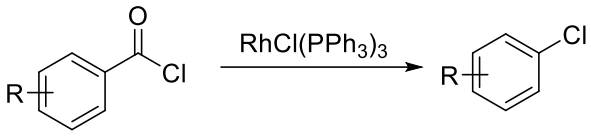
1-2-3 Utilization of Acyl Chlorides as a Halide Source

The utilization of acyl chlorides as a halide source was also disclosed in transition-metal-catalyzed reactions such as chlorination and addition reaction.

1-2-3-1 Decarbonylative Chlorination

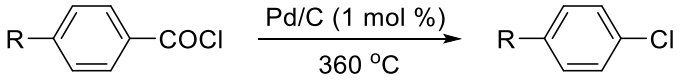
Blum firstly demonstrated rhodium-catalyzed decarbonylative chlorination of acyl chlorides to aryl chlorides. It provided a new strategy to transform easily available acyl chlorides to valuable products (Scheme 1-45).[51] The reaction temperature was set at the boiling point of acyl chlorides, which is the key for this transformation.

Scheme 1-45



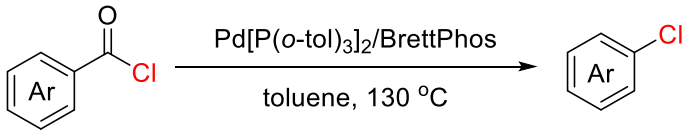
After that, palladium-catalyzed reaction of acyl chlorides in a decarbinylative manner was reported. The electron-withdrawing group-substituted acyl chloride and neutral acyl chloride gave the superior results than acyl chlorides with electron-donating groups (Scheme 1-46).[52]

Scheme 1-46



Recently, Sanford and co-workers reported Pd-catalyzed decarbonylative chlorination of acyl chlorides, in which various aryl chlorides were obtained in moderate to excellent yields (Scheme 1-47).[53] The subsequent addition of a nucleophile/base enables the one-pot conversions of these carboxylic acid derivatives to form C−C, C−N, C−O, C−S, C−B, and C−CF_3 bonds.

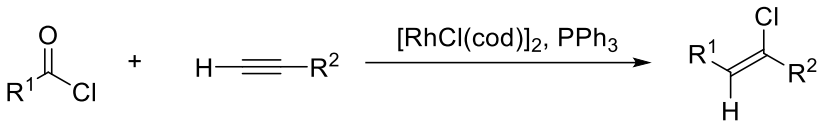
Scheme 1-47



1-2-3-2 Addition Reactions

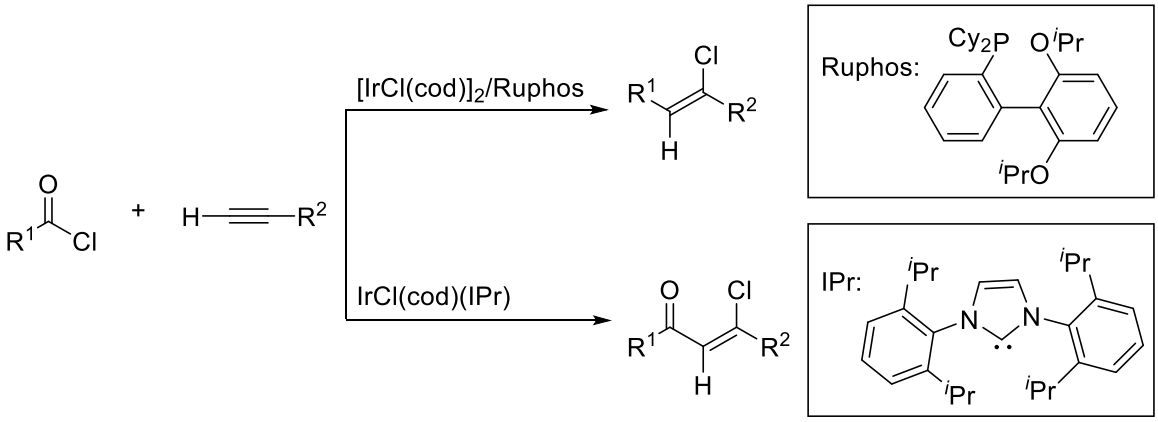
In 1996, Miura and co-workers reported Rh-catalyzed reactions of acyl chlorides with terminal alkynes, in which the corresponding vinyl chlorides were obtained in good yields with high regio- and stereoselectively (Scheme 1-48).[54]

Scheme 1-48



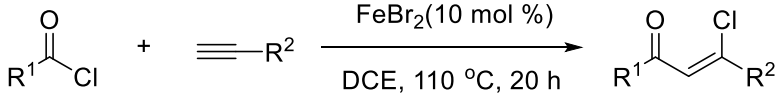
Tsuji *et al*. reported iridium-catalyzed selective addition of aromatic acyl chlorides to terminal alkynes. (*Z*)-*β*-Chloro-*α,β*-unsaturated ketones were obtained when IPr was used as the ligand, whereas when RuPhos as the ligand, (*Z*)-vinyl chlorides were formed (Scheme 1-49).[55]

Scheme 1-49



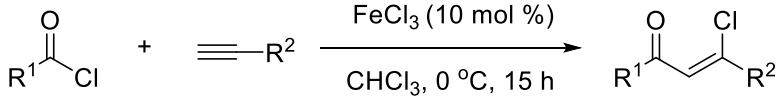
Li and Wang *et al*. disclosed the iron-catalyzed regio- and stereoselective addition of acid chlorides to alkynes. *β*-Chloro-*α,β*-unsaturated ketones were formed in dichloroethane at 110 ℃ for 20 h in good to excellent yields (Scheme 1-50).[56] The addition of acid chlorides to alkynes is atom-economical, since both carbonyl and chlorine moieties can be introduced into unsaturated compounds simultaneously.

Scheme 1-50



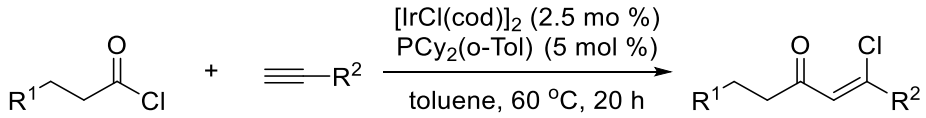
Mild reaction conditions for addition of acid chlorides to alkynes were developed by Cheng *et al*. They used easily available starting materials, a cheap and non-toxic catalyst to synthesize *β*-chlorovinyl ketones in a simple and efficient way (Scheme 1-51).[57]

Scheme 1-51



Tsuji *et al*. succeed in the addition of aliphatic acyl chlorides to terminal alkynes, when a combination of an irridium with dicyclohexyl(2-methylphenyl)phosphine (PCy_2(o-Tol)) catalyst system was used. Noteworthy is that the major intrinsic problems in transition-metal-catalyzed reactions, i.e., decarbonylation and *β*-hydrogen elimination, were not observed in this reaction (Scheme 1-52).[58]

Scheme 1-52



1-3 Comparison of Acyl Chlorides with Acyl Fluorides

Recently, acyl fluorides as analog of acyl chlorides have drawn much attention, because they show a unique nature in TM-catalyzed coupling reactions. Acyl fluorides can be synthesized from carboxylic acids[59] or acyl chlorides.[60] Acyl chlorides and fluorides have the similar structure, and in some cases they show similar behaviors. The difference of a halide moiety shows different properties in transition-metal-catalyzed reactions.

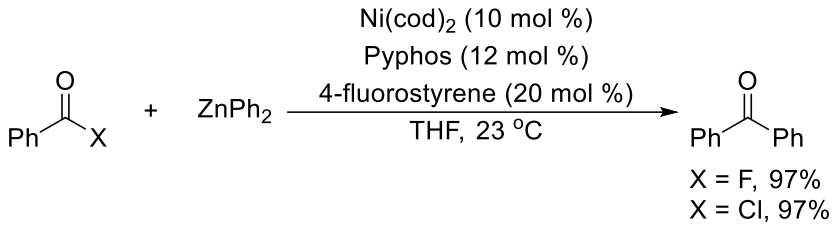
1-3-1 Similarity of Acyl Chlorides and Acyl Fluorides

Due to acyl chlorides and fluorides having the similar structure, in most reported cases they show comparable properties.

(1) Coupling with Organozinc

Zhang and Rovis developed an efficient protocol for ketone synthesis by nickel-catalyzed cross-coupling of carboxylic acid derivatives with organozinc reagents. Both acyl fluoride and chloride could react with Ph_2Zn to produce benzophenone in 97% yield (Scheme 1-53).[61]

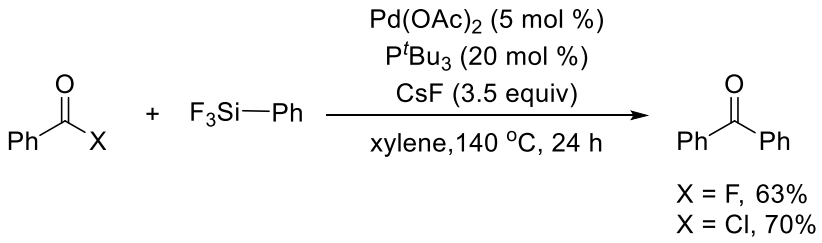
Scheme 1-53



(2) Coupling with Organosilicon

Both acyl chlorides and fluorides can be applied in palladium-catalyzed Hiyama coupling reaction with arylsilanes and could provide comparable yields. As a result, a variety of unsymmetrical benzophenone derivatives can be prepared with this method (Scheme 1-54).[62]

Scheme 1-54

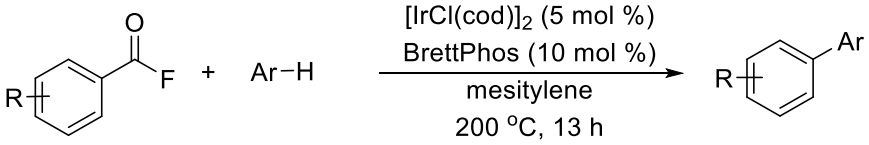


1-3-2 Difference of Acyl Chlorides and Acyl Fluorides

Although acyl chlorides and fluorides have the similar structure, they show significantly different behaviors in same transition-metal-catalyzed reactions.

In 2018, Tobisu *et al*. reported iridium-catalyzed decarbonylative arylation of acyl fluorides with (hetero)arenes through C–H bond cleavage. This reaction only worked with acyl fluorides, whereas no reaction occurred when acyl chlorides were used (Scheme 1-55).[63]

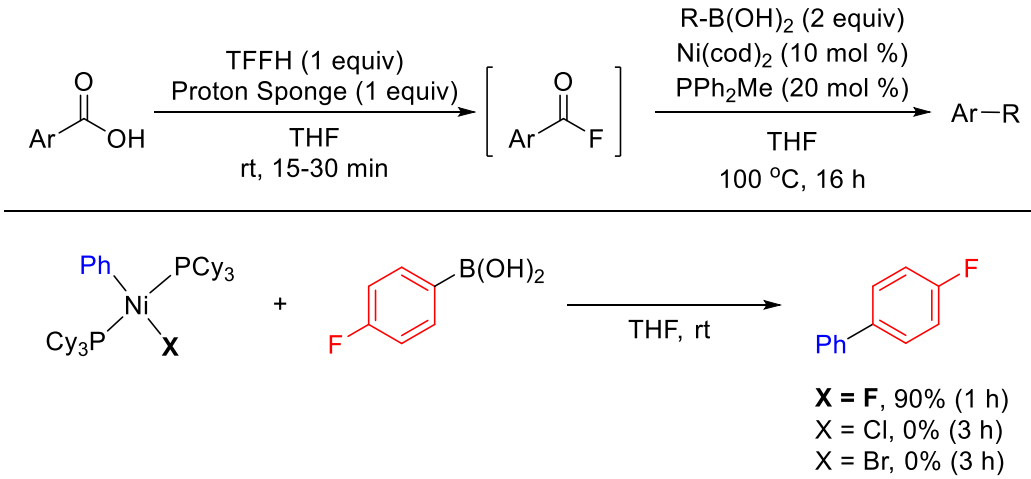
Scheme 1-55



Sanford and co-workers disclosed Ni-catalyzed decarbonylative arylation of acyl

fluorides with organoboron and organotin reagents. This report indicated that the oxidative addition product *trans*-NiPh(F)(PCy_3)$_2$ from acyl fluorides with the nickel catalyst could cause a ligand exchange with organoboron compounds whereas *trans*-NiPh(X)(PCy_3)$_2$ (X = Cl or Br) could not undergo the transmetalation progress, which showed the different reactivity of acyl fluorides and acyl chlorides (Scheme 1-56).[64]

Scheme 1-56



1-4 Summary

In this Chapter, the Author mainly involved the couplings of acyl chlorides in various aliphatic and aromatic ketone synthesis without a CO loss, particularly coupled with organometallic reagents. Although transformations of acyl chlorides in a decarbonylative manner were studied, the precious metal catalysts were required to facilitate the transformations. Besides, since acyl chlorides and acyl fluorides show some similarities and differences in the transition-metal-catalyzed reactions, the comparative studies of these acyl halides are of interest.

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CHAPTER 2

Nickel-Catalyzed Decarbonylative Cyanation of Acyl Chlorides

2-1. Introduction

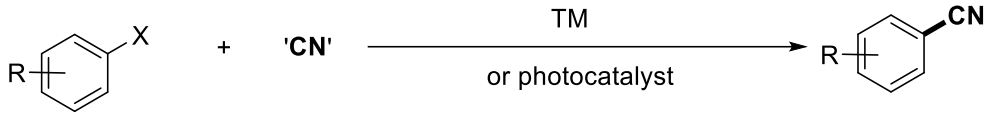
Nitriles are prevalent in natural products, pharmaceuticals, agrochemicals, dyes, and herbicides,[1] as well as important intermediates.[2] In this Chapter, the synthesis of nitriles via decarbonylative manner are systematically introduced. In generally, arylnitriles can be obtained via classical methods of Sandmeyer[3] and Rosenmund-von Braun[4] reactions by treatment of diazonium salts or aryl halides with CuCN and various synthetic routes to arylnitriles were further developed.[5-7] Alternatively, transition-metal (TM)-catalyzed nucleophilic cyanation of "preactivated" aryl halides[8] and phenol derivatives[9] or electrophilic cyanation of organometallic reagents[10] with various CN sources have well been developed (Scheme 2-1a). Higher atom-economy cyanation of arene C−H bonds by TM-catalyzed,[11] -mediated,[12] or photo-induced[13] reactions with the aid of suitable directing groups or electron-rich (hetero)arenes have been achieved.

On the other hand, carboxylic acids are potential candidates as electrophiles, because they are natural abundant and readily available.[14] However, direct transformation of carboxylic acids and their derivatives to nitriles have various drawbacks, e.g., requirement of additional preparatory steps, use of excess reagents, harsh conditions, and narrow range substrates.[15] Recently, two pioneering studies on decarbonylative cyanation have been disclosed (Scheme 2-1b). Szostak demonstrated Pd-catalyzed decarbonylative cyanation of amides with $Zn(CN)_2$, affording a wide range of arylnitriles.[16] Subsequently, Rueping developed the Ni-catalyzed cyanation of phenolic esters or amides with $Zn(CN)_2$.[17] Notably, all the starting materials, amides and esters, in the above-mentioned reactions are prepared from the corresponding acyl chlorides. Therefore, a direct synthesis of nitriles by decarbonylative cyanation of acyl chlorides is of great interest because acyl chlorides are commercially available or could be easily prepared from corresponding carboxylic acids.[18]

In this Chapter, the Author introduced nickel-catalyzed decarbonylative cyanation of acyl chlorides. This synthetic strategy proves to be more facile and atom economic than previous methods. Moreover, the step-by-step experimental studies revealed that the reaction sequences of the present catalytic reaction are oxidative addition, transmetalation, decarbonylation, and reductive elimination.

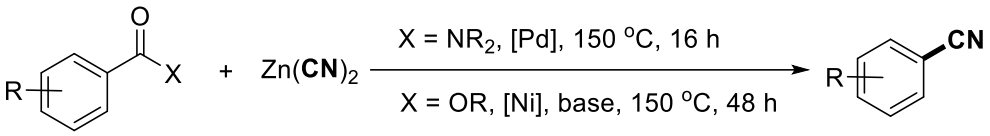
Scheme 2-1. Synthetic Routes of Nitriles.

(a) Conventional synthetic methods of arylnitriles



X = I, Br, Cl, OTf, OMs, $OCONMe_2$, OCO^tBu
MgBr, BR_2, SiR_3, or H

(b) Pd or Ni-catalyzed decarbonylative cyanation of carboxylic acid derivatives

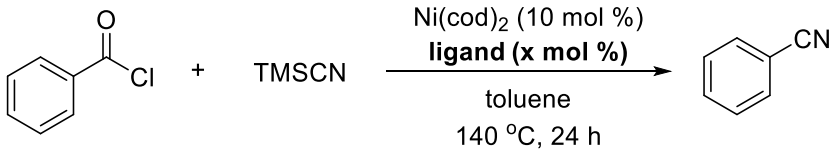


2-2. Results and Discussion

2-2-1 Optimization of Nickel-Catalyzed Cyanation Reaction

We commenced the model reaction of benzoyl chloride (**1a**) with trimethylsilyl cyanide (TMSCN, **2**) as the substrates. Various phosphine ligands were screened, bidentate ligand DPPE give 80% of **3a** (Table 2-1, entry 3), other bidentate ligands give poor results. To our delight, mono-dentated ligand PPh_3 show the highest reactivity, **3a** was obtained in 85% GC yield (entry 10). Monodentate phosphine ligands such as PEt_3, P^nBu_3, or PCy_3 was found to be inferior (entries 7-9). These ligand effect indicates that less electron-donating phosphine ligands are highly suitable for the present reaction regardless of the cone angles. The yield was increased to 99% by decreasing the amount of TMSCN to 1.2 equivalent (entry 15). Further screening the reaction conditions found 20 mol % of PPh_3 also could provide 97% of **3a** (entry 17).

Table 2-1. Screening of Ligands.



1a (0.2 mmol) **2** (2 equiv) **3a**

entry[a]	ligand (x mol %)	yield of **3a** (%)[b]
1	DCyPE (20)	5

2	DPPM (20)	10
3	DPPE (20)	80
4	DPPP (20)	20
5	DPPF (20)	49
6	Xantphos (20)	44
7	P^nBu_3 (40)	0
8	PEt_3 (40)	0
9	PCy_3 (40)	2
10	PPh_3 (40)	85
11[c]	PPh_3 (40)	53
12[d]	PPh_3 (40)	56
13[e]	PPh_3 (40)	86
14	PPh_3 (50)	90
15[f]	PPh_3 (40)	>99
16[f]	PPh_3 (30)	95
17[f]	PPh_3 (20)	97
18[f]	PPh_3 (10)	91

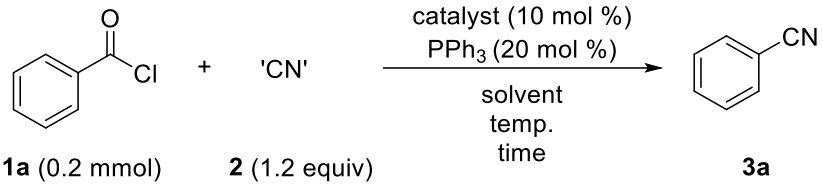
[a]Standard condition: **1a** (0.2 mmol), **2** (0.4 mmol) and $Ni(cod)_2$ (0.02 mmol) in toluene (1.0 mL) at 140 °C for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. [c]KF (2.5 equiv). [d]Toluene (0.5 mL). [e]150 °C. [f]TMSCN (1.2 equiv).

DCyPE DPPF Xantphos

After extensive optimization of reaction parameters (Tables 2-2), an inexpensive catalytic system of $Ni(cod)_2$ and PPh_3 effectively facilitated the decarbonylative cyanation of **1a** to afford benzonitrile (**3a**) in 80% isolated yield (entry 21). Notably, the exogenous base was not necessary, and this transformation could afford satisfying yields of the corresponding nitriles at 110 °C within 1 h. Previously reported palladium or nickel-catalyzed decarbonylative cyanation of carboxylic acid derivatives required the extended reaction time (16 to 48 h), and high temperature (150 °C).[16,17] $Zn(CN)_2$ that

has been successfully used in Ni or Pd-catalyzed decarbonylative cyanation reaction[16,17] gave no products. This reaction did not proceed in the absence of the Ni catalyst or PPh_3 ligand (entries 34 and 35). Since no formation of benzoyl cyanide was detected, the highly selective formation of **3a** rather than benzoyl cyanide might be a consequence of unfavorable reductive elimination between the benzoyl group and the cyano group, both of them are electron-poor ligands. Decarbonylation triggered reductive elimination between an electron-rich aryl ligand and an electron-deficient cyano ligand by a favorable electronic synergy.

Table 2-2. Screening of Temperature and Reaction Time.



entry[a]	catalyst	'CN'	temp. (°C)	time (h)	solvent	yield of **3a** (%)[b]
1	$Ni(cod)_2$	TMSCN	140	24	toluene	97
2	$Ni(cod)_2$	TMSCN	130	24	toluene	>99
3	$Ni(cod)_2$	TMSCN	120	24	toluene	88
4	$Ni(cod)_2$	TMSCN	110	24	toluene	88
5	$Ni(cod)_2$	TMSCN	130	8	toluene	>99
6	$Ni(cod)_2$	TMSCN	130	3	toluene	>99
7	$Ni(cod)_2$	TMSCN	130	1	toluene	>99
8	$Ni(cod)_2$	TMSCN	120	1	toluene	89
9	$Ni(cod)_2$	TMSCN	130	0.5	toluene	>99
10	$Ni(cod)_2$	TMSCN	130	0.17 (= 10 min)	toluene	99
11	$Ni(cod)_2$	$K_4Fe(CN)_6$	130	0.17 (= 10 min)	toluene	0
12	$Ni(cod)_2$	NaCN	130	0.17 (= 10 min)	toluene	0
13	$Ni(cod)_2$	KCN	130	0.17 (= 10 min)	toluene	0
14	$Ni(cod)_2$	CuCN	130	0.17 (= 10 min)	toluene	5
15	$Ni(cod)_2$	$Zn(CN)_2$	130	0.17 (= 10 min)	toluene	3
16	$Ni(cod)_2$	EtOC=OCN	130	0.17 (= 10 min)	toluene	0
17[c]	$Ni(cod)_2$	TMSCN	130	0.17 (= 10 min)	toluene	66
18	$Ni(cod)_2$	TMSCN	130	0.17 (= 10 min)	-	0

19	$Ni(cod)_2$	TMSCN	110	0.17 (= 10 min)	toluene	55
20	$Ni(cod)_2$	TMSCN	110	0.5	toluene	83
21	$Ni(cod)_2$	TMSCN	110	1	toluene	87 (80)
22	$Ni(cod)_2$	TMSCN	110	3	toluene	87
23	$Ni(cod)_2$	TMSCN	110	6	toluene	88
24	$Ni(cod)_2$	TMSCN	110	12	toluene	88
25	$Ni(cod)_2$	TMSCN	110	24	toluene	88
26	$NiCl_2$	TMSCN	110	1	toluene	0
27	$NiBr_2$	TMSCN	110	1	toluene	0
28	$Ni(acac)_2$	TMSCN	110	1	toluene	0
29	$Pd(OAc)_2$	TMSCN	110	1	toluene	0
30	$Pd(PPh_3)_4$	TMSCN	110	1	toluene	4
31	$Ni(cod)_2$	TMSCN	110	1	THF	33
32	$Ni(cod)_2$	TMSCN	110	1	1,4-dioxane	84
33	$Ni(cod)_2$	TMSCN	110	1	octane	71
34	-	TMSCN	110	1	toluene	0
35[e]	$Ni(cod)_2$	TMSCN	110	1	toluene	0

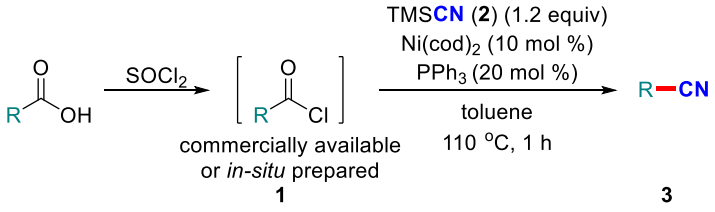
[a]Standard condition: **1a** (0.2 mmol), **2** (0.24 mmol), catalyst (0.02 mmol) and PPh_3 (0.04 mmol) in solvent (1.0 mL). An isolated yield was shown in parentheses. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. [c]Toluene 0.5 mL. [e]Without PPh_3.

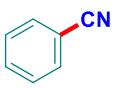
2-2-2 Nickel-Catalyzed Decarbonylative Cyanation of Acyl Chlorides

The optimized reaction conditions were applied for various acyl chlorides and the results were summarized in Table 2-3. It is noteworthy that the utilization of acyl chlorides were not only commercially available but in-situ prepared from corresponding carboxylic acids for one-pot protocol (denotes as footnote *d*), which demonstrated practicability of the present transformation. Initially, a qualitative assessment of the electronic trend of the decarbonylative cyanation reaction was examined. Electron-donating alkyl groups installed in the *para*-position of acyl chloride could give the corresponding nitriles **3b**-**3d** in 90-96% yields. When the substrates bearing ether **3f**-**3h** and acetal **3i** groups were employed, the higher temperature (150 ºC) was required to gain satisfying results. Methylthio (**3j**), methoxycarbonyl (**3k**), phenoxycarbonyl (**3l**),

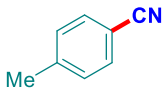
and benzoyl (**3m**) groups were well tolerated to give the desired products in good to excellent yields. On the other hand, a series of electron-deficient *para*-substituted acyl chlorides having trifluoromethyl, cyano, and halogens smoothly proceeded at 110 ºC within 1 h, forming **3n**-**3s** in 82-96% yields. Although bromide and iodide are known to be reactive for oxidative addition to nickel catalysts, they were compatible during the reactions. The steric hindrance of *ortho*-substituents was also productive for the formation of arylnitriles **3u** and **3v**, regardless of the electronic nature of the substituents. Even more sterically hindered 2,4,6-trimethylbenzoyl chloride (**1w**) was efficiently converted into **3w** in 94% yield. At the elevated temperature, fused aromatic acyl chlorides (**1x**-**1z**) could be incorporated and gave the corresponding arylnitriles in 80-87% yields. It should be noted that heteroatom-containing acyl chlorides also participated in the reaction, furnishing the desired nitriles **3aa** and **3ab** in 99% and 96% yields, respectively. Strikingly, the reaction scope could be readily extended to the synthesis of *α,β*-unsaturated nitriles (**3ac**). More surprisingly, secondary (**1ad**) and tertiary (**1ae**) alkylated acyl chlorides were proved to be an ideal coupling partner, although primary counterparts were unsuccessful; lauroyl chloride gave only 17% of the corresponding nitrile under standard conditions.

Table 2-3. Nickel-Catalyzed Decarbonylative Cyanation.[a,b]

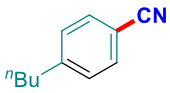




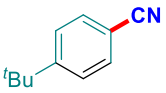
3a, 80%



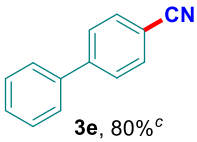
3b, 90%



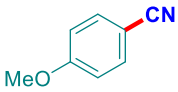
3c, 94%



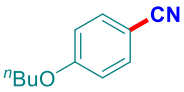
3d, 96%



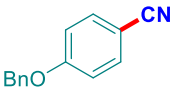
3e, 80%[c]



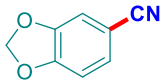
3f, 84%[c]



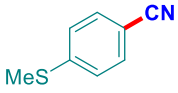
3g, 84%[c]



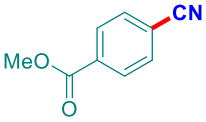
3h, 90%[cd]



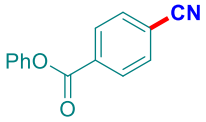
3i, 93%[cd]



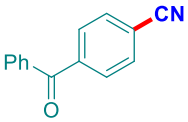
3j, 98%[d]



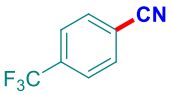
3k, 88%



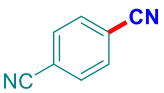
3l, 93%[cd]



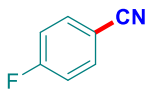
3m, 85%[d]



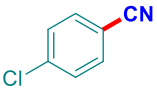
3n, 94%



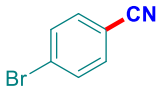
3o, 82%



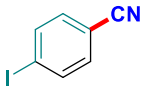
3p, 85%



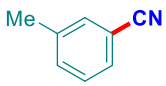
3q, 96%



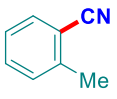
3r, 93%



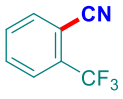
3s, 92%[e]



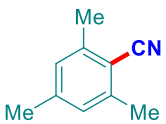
3t, 86%



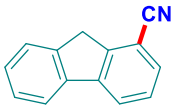
3u, 88%



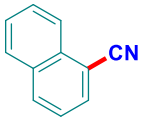
3v, 85%



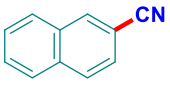
3w, 94%



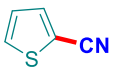
3x, 87%[cd]



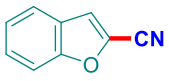
3y,82%[c]



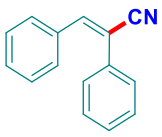
3z, 80%[c]



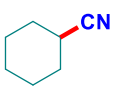
3aa, 99%



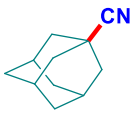
3ab, 96%[d]



3ac, 80%[df]
(*E*/*Z* = 94:6)



3ad, 86%[c]



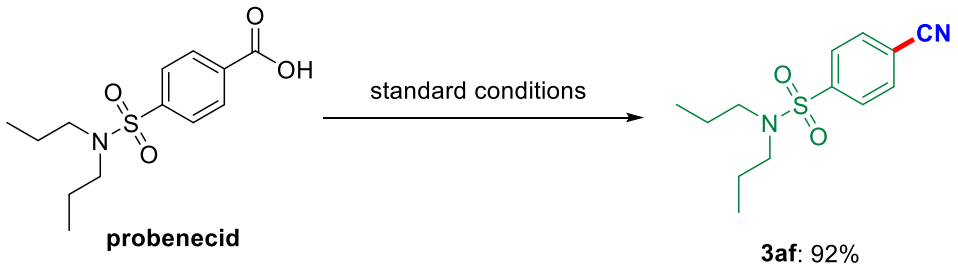
3ae, 88%[c]

[a]Reaction conditions: Acyl chlorides **1** (0.2 mmol), TMSCN (**2**, 0.24 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.04 mmol), toluene (1 mL), 110 ºC, 1 h. [b]Isolated yield. [c]150 ℃, 1 h. [d]The *in-situ* prepared acyl chlorides **1** from the corresponding carboxylic acids (0.2 mmol) were used. [e]80 ℃, 1 h. [f]**1ac** (*E*/*Z* = 94:6) was used.

To demonstrate the synthetic utility of the present reaction, decarbonylative cyanation of biologically active compounds were conducted. Cyanation of probenecid,[19] carboxylic acid-containing drug, was viable and gave **3af** in 92% yield (Scheme 2-2a). A key intermediate in the synthesis of sartan derivatives,[20] 2-(4-tolyl)benzonitrile (**3ag**) was isolated in 98% yield (Scheme 2-2b). Besides, we succeeded in late-stage modification of a bioactive estrone derivative. The etherification of estrone with **4**, followed hydrolysis of **5** afforded carboxylic acid **6**. Finally, compound **6** was subjected to the decarbonylative cyanation to provide **3ah** in 74% yield (Scheme 2-2c).

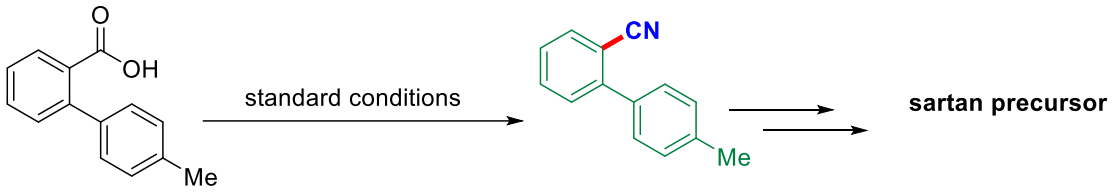
Scheme 2-2. Synthetic Applications.

a) Decarbonylative cyanation of probenecid



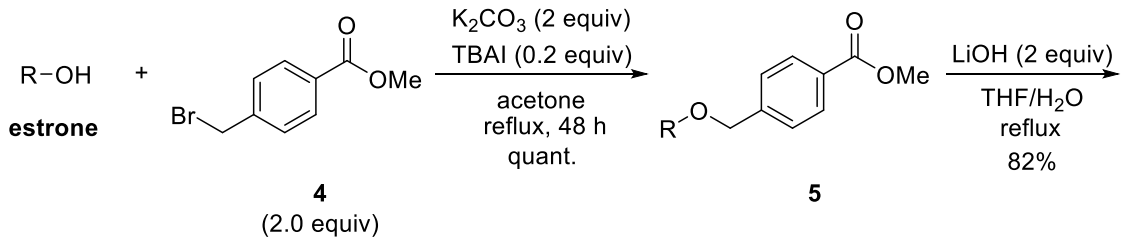
probenecid **3af**: 92%

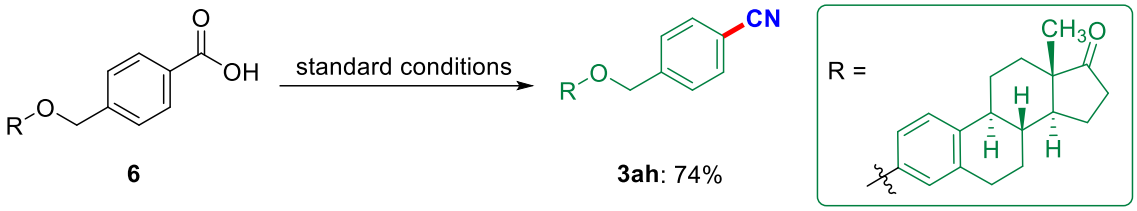
b) Decarbonylative cyanation for the synthesis of sartan precursor



3ag: 98%

c) Late-stage decarbonylative cyanation of estrone derivative





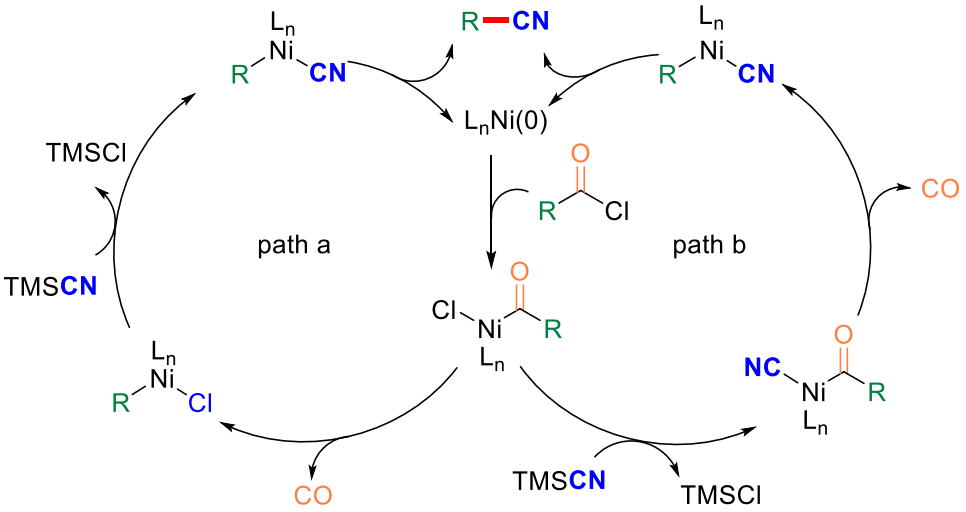
[a]Standard conditions: Carboxylic acid (0.2 mmol), $SOCl_2$ (2 equiv), DMF (5 μL), CH_2Cl_2 (0.8 mL), rt, 12 h. Volatiles were removed under vacuum, then **2** (0.24 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.04 mmol), toluene (1 mL), 150 ºC, 1 h.

2-2-3 Mechanistic Studies

Although various types of transition-metal-catalyzed decarbonylative cross-coupling reactions have been further explored, mechanism about the reaction sequences is still under debate. Thereby, there are two possible reaction pathways for the present reaction (Scheme 2-3). In both pathways, the reaction is initiated by oxidative addition of acyl

chloride to Ni(0) forming acyl(chloro)nickel(II) species[21] and the final reductive elimination affording the product. In path a, CO elimination takes place prior to transmetalation with TMSCN, which was supported by Shi[22] and Sanford.[23] They conducted stoichiometric reactions to isolate acyl(halogeno)nickel(II) complexes, leading to a smooth decarbonylation process. In addition, theoretical calculations performed by Szostak also illustrated that acylpalladium species is prone to decarbonylation.[24] Alternatively, path b involves the reaction sequences of transmetalation of acyl(chloro)nickel(II) complex with TMSCN prior to decarbonylation. Ritter[25] has also shown experimental evidence for supporting path b by isolation of the intermediate complexes in the Pd-catalyzed decarbonylative difluoromethylation. Furthermore, Itami,[26] Rueping,[27] and Schoenebeck[28] performed DFT calculations, in which a lower energy barrier is required for a smooth decarbonylation of the intermediates than transmetalation.

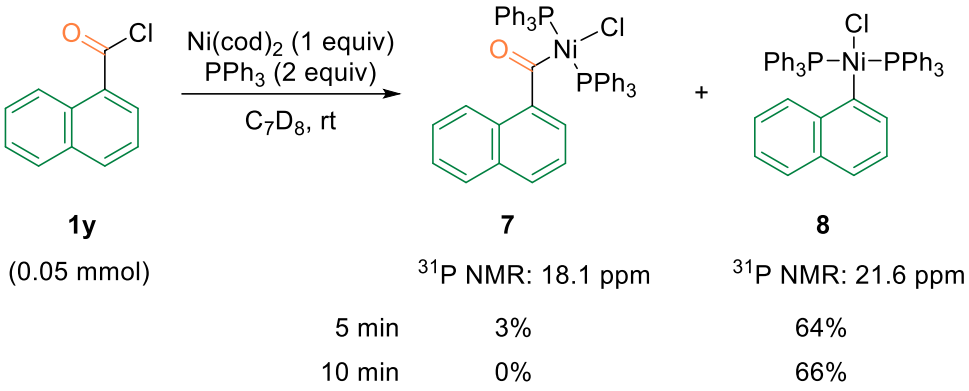
Scheme 2-3. Two Possible Reaction Pathways



To clarify which pathway in Scheme 2-3 is more favorable, we carried out some stoichiometric reactions. First, the reaction of $Ni(cod)_2$ and 2 equiv of PPh_3 with 1-naphthoyl chloride (**1y**) in C_7D_8 was monitored by the $^{31}P\{^1H\}$ NMR measurements at room temperature (Scheme 2-4). After 5 min, a singlet at δ 18.1 assigned to acyl(chloro)nickel(II) complex **7** was observed in only 3% yield, which completely disappeared after 10 min, while 64% of aryl(chloro)nickel(II) complex **8** (δ 21.6) and 33% of $Ni(CO)_2(PPh_3)_2$ (δ 32.9) were detected. This result suggests that both oxidative

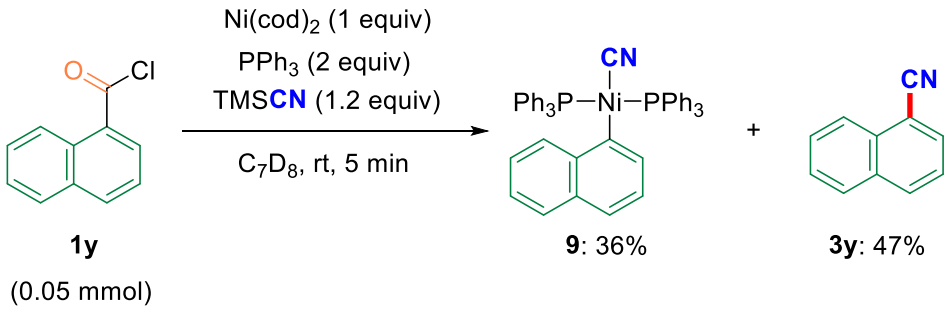
addition and subsequent decarbonylation can readily occur due to a weak coordination ability of PPh_3, which possesses an open coordination site which is able to accept the carbonyl ligand.

Scheme 2-4. Reaction of $Ni(cod)_2$/2 Equivalents of PPh_3 with **1y** in the Absence of TMSCN.



Given that no reaction took place between **1y** with TMSCN, we performed the identical reaction in the presence of TMSCN at room temperature (Scheme 2-5). After 5 min, complex **9** was detected in 36% NMR yield, along with the formation of **3y** in 47% yield, suggesting that the rates of both transmetalation and decarbonylation are faster than that of reductive elimination, leading to the product **3y**.

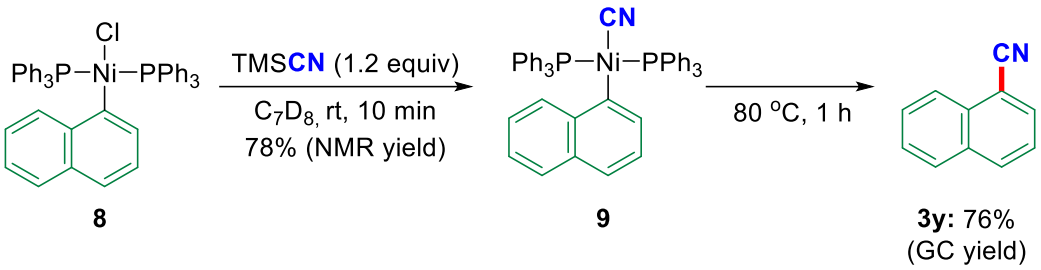
Scheme 2-5. Reaction of $Ni(cod)_2$/2 Equivalents of PPh_3 with **1y** in the Presence of TMSCN.



Alternatively, complex **9** was prepared by the reaction of the once prepared complex **8**, derived from the reaction of $Ni(cod)_2$, 2 equivalents of PPh_3, and **1y**, with TMSCN. Heating the toluene solution of complex **9** at 80 ℃ for 1 h smoothly afforded **3y** in 76% yield through reductive elimination (Scheme 2-6). When the same reaction was conducted in the presence of 2 equivalents of PPh_3, the yield of the product **3y** was dropped to 50%. These results strongly support that the reductive elimination takes place

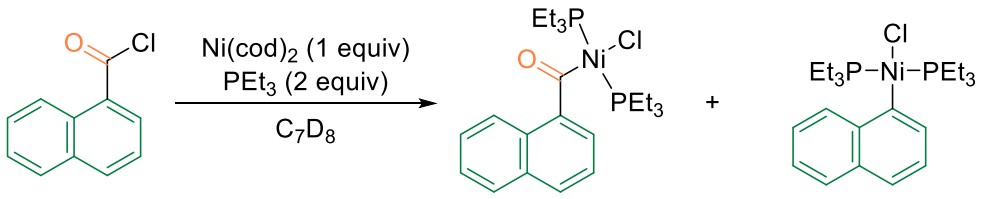
by ligand dissociation to form three-coordinate complex rather than proceeds from a four-coordinate intermediate.

Scheme 2-6. Synthesis and Reductive Elimination of Complex **9**.



To verify the effect of the phosphine ligands, we conducted the identical stoichiometric reactions using PEt_3 (Scheme 2-7). Similarly, oxidative addition of **1y** to nickel was completed at room temperature within 5 min and acyl(chloro)nickel(II) complex **10** was observed in 91% yield, along with aryl(chloro)nickel(II) complex **11** in 9% yield. Although this solution was kept for 12 h, 75% of complex **10** was still remained intact. The same reaction was conducted at 50 °C, but no further decarbonylation occurred even after 5 h. These results indicate the presence of an equilibrium between **10** and **11** and relatively unfavorable decarbonylation from **10** rather than **7**.

Scheme 2-7. Reaction of $Ni(cod)_2$/2 Equivalents of PEt_3 with **1y** in the Absence of TMSCN.



rt	5 min	91%	9%
	12 h	75%	25%
50 °C	5 min	75%	19%
	5 h	56%	37%
	24 h	56%	38%

To our delight, acyl(chloro)nickel complex **10** could be isolated in 45% yield and its structure was unambiguously determined by X-ray analysis (Figure 2-1).

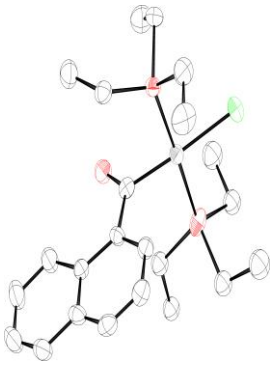
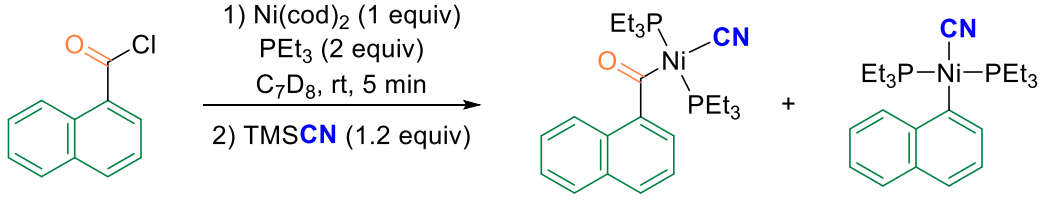


Figure 2-1. X-ray crystal structure of complex **10**. An ORTEP drawing with atoms at 50% probability. Hydrogen atoms are omitted for clarity. A PEt_3 ligand was treated as disordered.

Next, we investigated the reaction of the Ni(0) precursor with **1y** in the presence of TMSCN (Scheme 2-8). The mixture of $Ni(cod)_2$, 2 equiv of PEt_3, and **1y** in C_7D_8 was stirred at room temperature for 5 min. Upon addition of TMSCN, complex **10** was converted to produce complex **12** immediately in 66% yield. Complex **12** was then gradually converted to complex **13** in 27% yield via decarbonylation over 210 min, albeit with other unidentified major products bearing two PEt_3 ligands (22% combined yields). Besides, insoluble solid was observed at the bottom of an NMR tube. With the results shown in Schemes 2-7 and 2-8 in hand, with a PEt_3 ligand, we concluded that transmetalation with TMSCN is faster than decarbonylation.

Scheme 2-8. Transmetalation and Decarbonylation in the Presence of TMSCN.



1y (0.05 mmol)

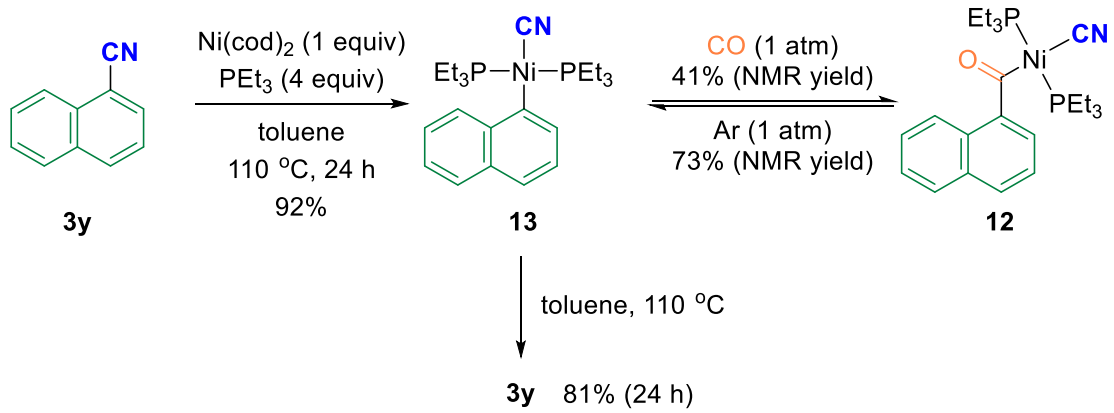
12 $^{31}P\{^1H\}$ NMR: 15.1 ppm

13 $^{31}P\{^1H\}$ NMR: 18.6 ppm

rt	2 min	66%	11%
	210 min	0%	27%

Complex **13** could also be synthesized by oxidative addition of **3y** to $Ni(cod)_2$/4 PEt_3 in 92% yield (Scheme 2-9). Upon heating complex **13** at 110 ℃ for 24 h, reductive elimination product **3y** was obtained in 81% yield. This observation is inconsistent with the fact that a catalytic reaction does not proceed when PEt_3 was employed, but the results of the stoichiometric reactions are sometimes different from its catalytic counterparts. Due to the robustness of the aryl(cyano)nickel(II) complex **13**, its X-ray analysis was successful (Figure 2-2). Treatment of the toluene solution of complex **13** with CO gas in a balloon, complex **12** was detected in 41% NMR yield, along with the remaining complex **13** in 36% yield, while upon the replacement of CO with Ar, complex **13** was recovered in 73% NMR yield, indicating that a decarbonylation process is reversible.

Scheme 2-9. Synthesis and Reactivity of Complex **13**.



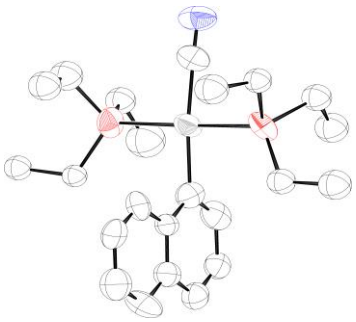
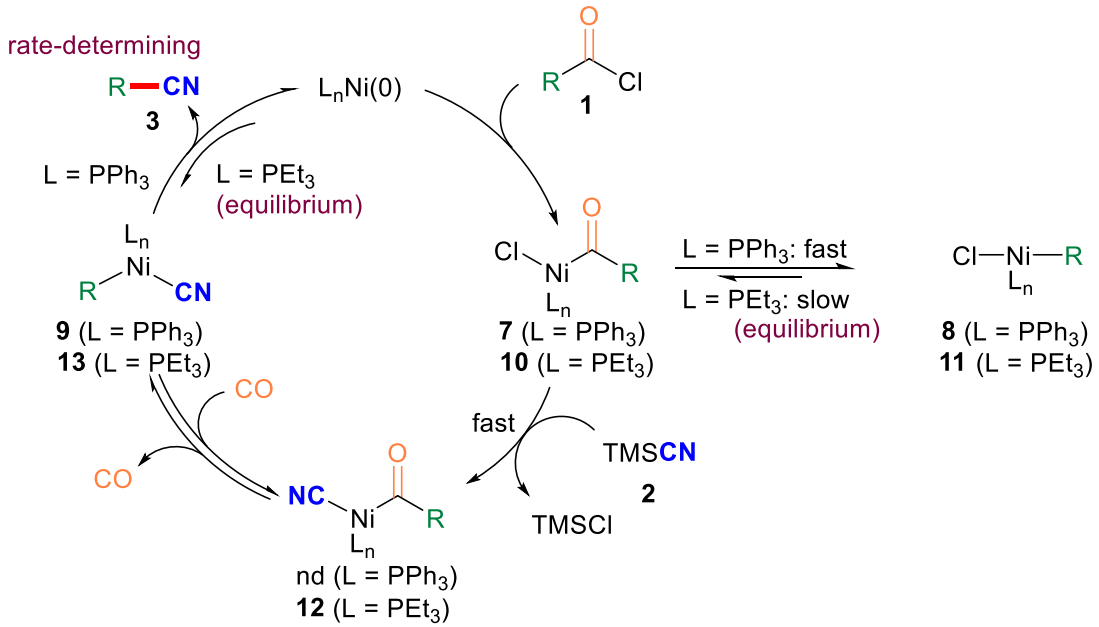


Figure 2. X-ray crystal structure of complex **13**. An ORTEP drawing with atoms at 50% probability. Hydrogen atoms were omitted for clarity. PEt_3 ligands were treated as disordered.

Based on our experimental studies, we propose the mechanism of the present reaction (Scheme 2-10). Initially, oxidative addition of acyl chlorides **1** to Ni(0) generates the acyl(chloro)nickel(II) intermediates **7** (L = PPh_3) or **10** (L = PEt_3). In the absence of **2**,

the reaction rate of decarbonylation of complex **7** leading to **8** is much faster than that of the conversion of complex **10** to **11**. While, in the presence of **2**, although both transmetalation and decarbonylation are too fast to detect in the PPh_3 system, transmetalation of acyl(chloro)nickel(II) **10** takes place to produce complex **12** prior to decarbonylation, forming complex **13** in the PEt_3 system. The fact that the life-time of complex **9** was observed to some extents suggests that reductive elimination might be a rate-determining step in the catalytic cycle, although other possibilities such as the CO loss to regenerate the active Ni(0) catalyst cannot be ruled out.

Scheme 2-10. Proposed Mechanism.



2-3. Summary

In summary, we have developed decarbonylative cyanation of easily available acyl chlorides under nickel catalysis. This reaction can readily transform a diversity of acyl chlorides into nitriles with a broad substrate scope and functional group tolerance. Detailed mechanistic studies clarified the sequences of the reaction in the catalytic cycle. The utilization of weaker coordinating PPh_3 ligand is crucial to facilitate both decarbonylation and reductive elimination steps.

2-4. Experimental Section

2-4-1 General Instrumentation and Chemicals

Unless otherwise noted, all the reactions were carried out under an argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 ºC) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using silica gel 60 N (spherical, neutral, 40-100 μm) from Kanto Chemicals Co., Inc. NMR spectra (^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} NMR, and ^{19}F{^{1}H}) were recorded on Varian INOVA-600 (600 MHz), Mercury-400 (400 MHz), or 300-NMR ASW (300 MHz) spectrometers. GC analyses were performed on a Shimadzu GC-14A equipped with a flame ionization detector using Shimadzu Capillary Column (CBP1-M25-025) and Shimadzu C-R6A-Chromatopac integrator. Infrared spectra were recorded on a Shimadzu IR Prestige-21 spectrophotometer. GC/MS analyses were carried out on a SHIMADZU GC-17A equipped with a SHIMADZU QP-5050 GCMS system. Elemental analyses were carried out with a Perkin-Elmer 2400 CHN elemental analyser at Okayama University.

All ^{1}H NMR chemical shifts were reported in ppm relative to proton resonance in $CDCl_3$ at δ 7.26, $(CD)_3SO$ at δ 2.50, CD_2Cl_2 at δ 5.32, $(CD)_3CO$ at δ 2.05. All ^{13}C{^{1}H} NMR chemical shifts were reported in ppm relative to carbon resonance in $CDCl_3$ at δ 77.16, $(CD)_3SO$ at δ 39.52, CD_2Cl_2 at δ 53.84, $(CD)_3CO$ at δ 29.84. The ^{31}P{^{1}H} chemical shifts were reported in ppm relative to external reference of H_3PO_4 at δ 0.00. The ^{19}F{^{1}H} NMR spectra were measured by using CCl_3F (δ = 0.00 ppm) as an external standard. The NMR yields were determined using dibromomethane as an internal standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

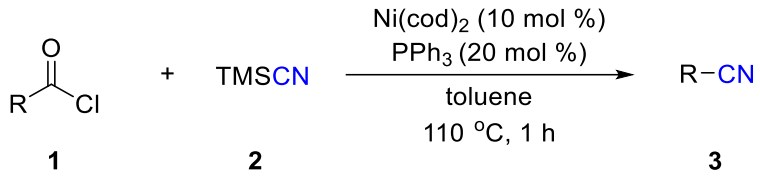
Chemicals

Unless otherwise noted, materials obtained from commercial suppliers were used

without further purification. Benzoyl chloride **1a** and trimethylsilyl cyanide **2** was purchased from TCI Co., Ltd. All acid chlorides were distilled before used. Bis(1,5-cyclooctadiene)nickel and triethylphosphine (1.0 M in THF) were purchased from Sigma-Aldrich Co. Triphenylphosphine was obtained from Nacalai Tesque,. *n*-Dodecane was purchased from Kanto Chemical Co., Inc.

2-4-2 Experimental Procedures

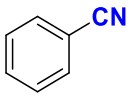
2-4-2-1 Ni-Catalyzed Decarbonylative Cyanation of Commercially Available Acyl Chlorides



1 **2** **3**

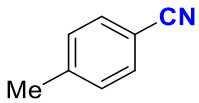
To a toluene (1 mL) solution of $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 10 mol %) and PPh_3 (10.5 mg, 0.04 mmol, 20 mol %) in an oven-dried Schlenk tube containing a stirring bar, were added acyl chlorides **1** (0.2 mmol) and TMSCN (**2**) (23.4 mg, 0.24 mmol, 1.2 equiv). The mixture was heated at 110 ºC with stirring for 1 h. After cooling to room temperature, the crude product was purified by column chromatography on silica gel or bulb-to-bulb distillation to afford the corresponding nitriles **3**.

Benzonitrile (3a)[16]



Colorless oil. Yield was 80% (16.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45-7.47 (m, 2H), 7.58-7.61 (m, 1H), 7.64 (d, J = 8.2 Hz, 2H).

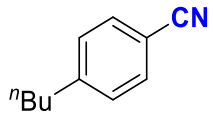
4-Methylbenzonitrile (3b)[16]



Colorless oil. Yield was 90% (21.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.40 (s, 3H),

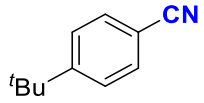
7.25 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H).

4-Butylbenzonitrile (3c)[9c]



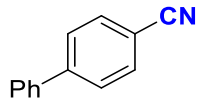
Colorless oil. Yield was 94% (29.9 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.93 (t, J = 7.4 Hz, 3H), 1.32-1.37 (m, 2H), 1.58-1.61 (m, 2H), 2.66 (t, J = 7.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 7.53-7.58 (d, J = 8.2 Hz, 2H).

4-(*Tert*-butyl)benzonitrile (3d)[17]



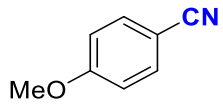
Colorless oil. Yield was 96% (30.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (s, 9H), 7.48 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H).

[1,1'-Biphenyl]-4-carbonitrile (3e)[16]



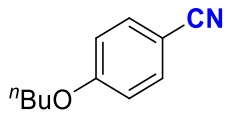
White solid. Yield was 80% (28.7 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41-7.44 (m, 1H), 7.47-7.50 (m, 2H), 7.58-7.60 (m, 2H), 7.68-7.70 (m, 2H), 7.72-7.74 (m, 2H).

4-Methoxybenzonitrile (3f)[16]



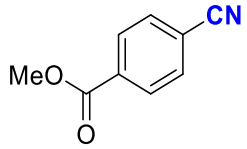
White solid. Yield was 84% (22.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.95 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 9.0 Hz, 2H).

4-Butoxybenzonitrile (3g)[29]



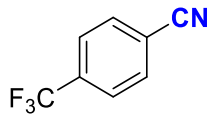
Colorless oil. Yield was 84% (29.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.98 (t, J = 7.4 Hz, 3H), 1.46-1.52 (m, 2H), 1.76-1.81 (m, 2H), 4.00 (t, J = 6.5 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 8.9 Hz, 2H).

Methyl 4-cyanobenzoate (3k)[16]



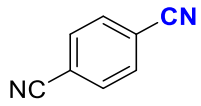
White solid. Yield was 88% (28.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H), 7.71-7.76 (d, J = 8.4 Hz, 2H), 8.11-8.15 (d, J = 8.4 Hz, 2H).

4-(Trifluoromethyl)benzonitrile (3n)[16]



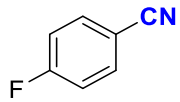
Colorless oil. Yield was 94% (32.2 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, J = 7.8 Hz, 2H), 7.79-7.83 (d, J = 7.8 Hz, 2H).

Terephthalonitrile (3o)[16]



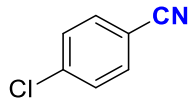
White solid. Yield was 82% (21.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 4H).

4-Fluorobenzonitrile (3p)[16]



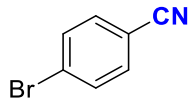
Colorless oil. Yield was 85% (20.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16-7.20 (m, 2H), 7.65-7.70 (m, 2H).

4-Chlorobenzonitrile (3q)[30]



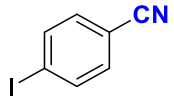
White solid. Yield was 96% (26.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45-7.48 (m, 2H), 7.58-7.61 (m, 2H).

4-Bromobenzonitrile (3r)[30]



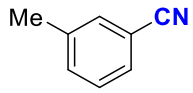
White solid. Yield was 93% (33.9 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50-7.55 (m, 2H), 7.62-7.65 (m, 2H).

4-Iodobenzonitrile (3s)[30]



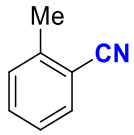
White solid. Yield was 92% (42.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.39 (m, 2H), 7.83-7.87 (m, 2H).

3-Methylbenzonitrile (3t)[16]



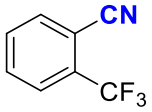
Colorless oil. Yield was 86% (20.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.39 (s, 3H), 7.35 (t, J = 8.4 Hz, 1H), 7.39-7.41 (d, J = 8.4 Hz, 1H), 7.44-7.47 (m, 2H).

2-Methylbenzonitrile (3u)[16]



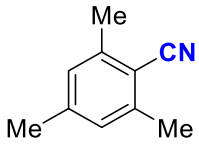
Colorless oil. Yield was 88% (20.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.55 (s, 3H), 7.25-7.29 (t, J = 7.8, 0.6 Hz, 1H), 7.32 (td, J = 7.8, 0.6 Hz, 1H), 7.48 (td, J = 7.8, 1.2 Hz, 1H), 7.60 (dd, J = 7.8, 1.2 Hz, 1H).

2-(Trifluoromethyl)benzonitrile (3v)[31]



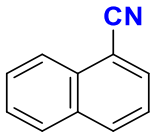
Yellow liquid. Yield was 85% (29.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (td, J = 7.6, 0.6 Hz, 1H), 7.75 (td, J = 7.6, 0.6 Hz 1H), 7.81 (dd, J = 7.8, 0.6 Hz, 1H), 7.86 (dd, J = 7.8, 0.6 Hz, 1H).

2,4,6-Trimethylbenzonitrile (3w)[17]



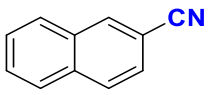
White solid. Yield was 94% (27.3 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.48 (s, 6H), 6.93 (s, 2H).

1-Naphthonitrile (3y)[17]



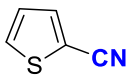
White solid. Yield was 82% (25.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53 (td, J = 7.5, 1.2 Hz, 1H), 7.63 (td, J = 7.8, 1.2 Hz, 1H), 7.71 (td, J = 7.8, 1.8 Hz, 1H), 7.93 (td, J = 7.2, 1.2 Hz 2H), 8.09 (d, J = 8.3 Hz, 1H), 8.25 (dd, J = 8.4, 0.6 Hz 1H).

2-Naphthonitrile (3z)[17]



White solid. Yield was 80% (24.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60-7.67 (m, 3H), 7.89-7.93 (m, 3H), 8.24 (s, 1H).

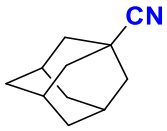
Thiophene-2-carbonitrile (3aa)[17]



White solid. Yield was 99% (21.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11-7.14 (m,

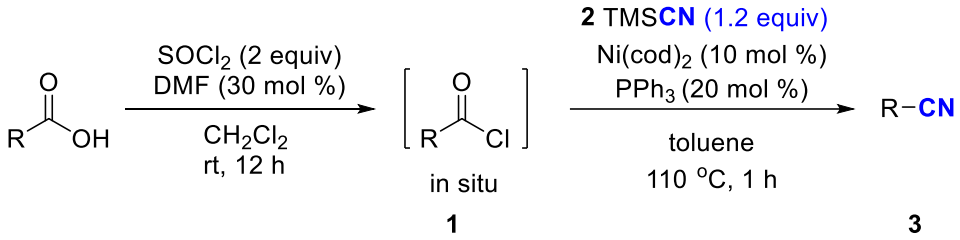
1H), 7.58-7.64 (m, 2H).

Adamantane-1-carbonitrile (3ae)[32]



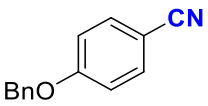
White solid. Yield was 88% (28.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.69-1.74 (m, 6H), 2.03 (s, 9H).

2-4-2-2 Ni-Catalyzed Decarbonylative Cyanation of Acyl Chlorides 1 in-situ Prepared from Carboxylic Acids



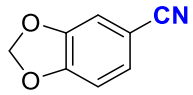
To the solution of anhydrous 1,2-dichloromethane (0.8 mL) and DMF (5 μL) of carboxylic acid (0.2 mmol) in an oven-dried Schlenk tube containing a stirring bar, was added dropwise thionyl chloride (47.6 mg, 0.4 mmol, 2 equiv) using a syringe. The reaction mixture was stirred at room temperature for 12 h. The solvent and unreacted thionyl chloride were removed under reduced pressure. The resulting acyl chloride was used without additional purification.[33] Then $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 10 mol %), PPh_3 (10.5 mg, 0.04 mmol, 20.0 mol %), toluene (1 mL), and TMSCN (23.4 mg, 0.24 mmol, 1.2 equiv) were successively added. The mixture was stirred at 110 ºC for 1 h. After cooling to room temperature, the crude product was purified by column chromatography on silica gel to afford the corresponding nitriles **3**.

4-(Benzyloxy)benzonitrile (3h)[34]



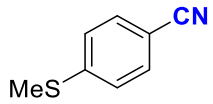
White solid. Yield was 90% (37.7 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.12 (s, 2H), 7.01-7.03 (m, 2H), 7.36-7.38 (m, 1H), 7.39-7.43 (m, 4H), 7.58-7.60 (m, 2H).

Benzo[d][1,3]dioxole-5-carbonitrile (3i)[9c]



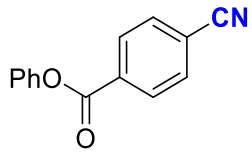
White solid. Yield was 93% (27.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.07 (s, 2H), 6.86 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 1.6 Hz, 1H), 7.21 (dd, J = 8.0, 1.6 Hz, 1H).

4-(Methylthio)benzonitrile (3j)[35]



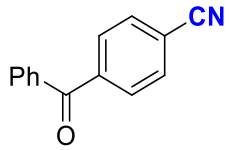
Colorless oil. Yield was 99% (29.3 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.51 (s, 3H), 7.26 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H).

Phenyl 4-cyanobenzoate (3l)[16]



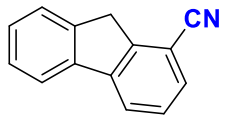
White solid. Yield was 93% (41.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21-7.23 (m, 2H), 7.30-7.33 (m, 1H), 7.44-7.47 (m, 2H), 7.81-7.83 (m, 2H), 8.30-8.32 (m, 2H).

4-Benzoylbenzonitrile (3m)[17]



White solid. Yield was 85% (35.2 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50-7.53 (m, 2H), 7.62-7.65 (m, 1H), 7.77-7.80 (m, 4H), 7.86-7.88 (m, 2H).

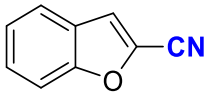
9H-fluorene-1-carbonitrile (3x)[36]



White solid. Yield was 87% (33.3 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.07 (s, 2H),

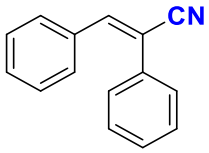
7.39 (td, J = 7.2, 1.2 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.57 (dd, J = 7.8, 1.2 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H).

Benzofuran-2-carbonitrile (3ab)[32]



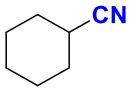
Yellow oil. Yield was 96% (27.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (ddd, J = 8.4, 7.1, 1.2 Hz, 1H), 7.47 (d, J = 0.9 Hz, 1H), 7.51 (ddd, J = 8.4, 7.1, 1.2 Hz, 1H), 7.56 (dd, J = 8.4, 1.2 Hz, 1H), 7.68 (dd, J = 7.9, 0.9 Hz, 1H).

(*E*)-2,3-Diphenylacrylonitrile (3ac)[37]



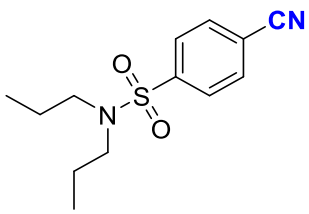
Yellow solid. Yield was 80% (32.8 mg). (*E*/*Z* = 96/4) ***E*-3ac** isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16-7.18 (m, 2H), 7.22-7.25 (m, 2H), 7.28-7.31 (m, 1H), 7.34-7.42 (m, 6H). ***Z*-3ac** isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45-7.48 (m, 6H), 7.56 (s, 1H), 7.69-7.71 (m, 2H), 7.90-7.92 (m, 2H).

Cyclohexanecarbonitrile (3ad)[38]



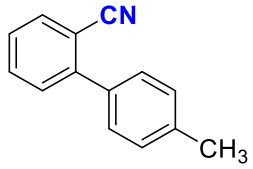
Colorless oil. Yield was 86% (18.8 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.41-1.53 (m, 4H), 1.66-1.75 (m, 4H), 1.83-1.85 (m, 2H), 2.60-2.63 (m, 1H).

4-Cyano-*N*,*N*-dipropylbenzenesulfonamide (3af)[39]



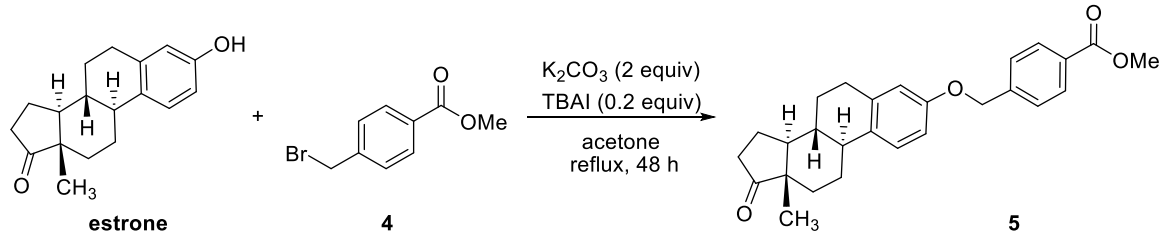
White solid. Yield was 92% (48.8 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85 (t, J = 7.8 Hz, 6H), 1.50-1.56 (m, 4H), 3.09 (t, J = 7.8 Hz, 4H), 7.78-7.80 (m, 2H), 7.90-7.91 (m, 2H).

4'-Methyl-[1,1'-biphenyl]-2-carbonitrile (3ag)[40]



Pale yellow solid. Yield was 98% (37.9 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.31 (d, J = 7.8 Hz, 2H), 7.42 (td, J = 7.8, 1.2 Hz, 1H), 7.47 (d, J = 7.8 Hz, 2H), 7.51 (dd, J = 7.8, 1.2 Hz, 1H), 7.63 (td, J = 7.8, 1.2 Hz, 1H), 7.76 (dd, J = 7.8, 1.2 Hz, 1H).

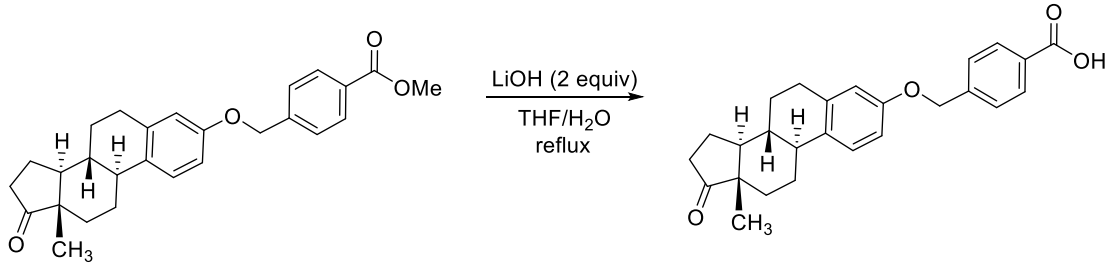
2-4-2-3 Ni-Catalyzed Decarbonylative Cyanation of Estrone Derivatives Synthesis of Methyl 4-((((8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17–decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl)benzoate (5)



Compound **5** was synthesized according to a modified procedure.[41] An oven-dried Schlenk tube containing a stirring bar was charged with estrone (270 mg, 1 mmol), compound **4** (458.2 mg, 2 mmol, 2 equiv), K_2CO_3 (276.4 mg, 2 mmol, 2 equiv), TBAI (73.9 mg, 0.2 mmol, 0.2 equiv) and acetone (10 mL). After the reaction mixture was heated to reflux for 48 h, the solvent was removed under vacuum. The crude mixture was extracted with dichloromethane (10 mL × 3) and organic layers was combined, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (eluent: 5:1 v/v hexane:EtOAc) to afford **5** quantitatively (418 mg) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.39-1.65 (m, 6H), 1.93-1.97 (m, 1H), 1.98-2.08 (m, 2H), 2.14 (dt, J = 19.0, 8.8 Hz, 1H), 2.23-2.28 (m, 1H), 2.37-2.41 (m, 1H), 2.50 (dd, J = 19.0, 8.8 Hz, 1H), 2.88-2.91 (m, 2H),

3.92 (s, 3H), 5.10 (s, 2H), 6.72 (d, J = 2.6 Hz, 1H), 6.77 (dd, J = 8.6, 3.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 8.05 (dd, J = 7.2, 1.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 14.0, 21.7, 26.0, 26.6, 29.8, 31.7, 36.0, 38.4, 44.1, 48.1, 50.5, 52.3, 69.4, 112.4, 115.0, 126.5, 127.0, 129.6, 130.0, 132.7, 138.0, 142.6, 156.6, 167.0, 221.1. FT-IR (KBr): 2934, 2910, 2859, 2830, 1734, 1719, 1605, 1499, 1454, 1437, 1414, 1279, 1254, 1236, 1175, 1109, 1036 cm^{-1}. HRMS (FAB^+): Calcd for $C_{27}H_{30}O_4$: 418.2144. Found: 418.2150. Anal. Calcd for $C_{27}H_{30}O_4$: C, 77.48; H, 7.23%. Found: C, 77.41; H, 7.25%.

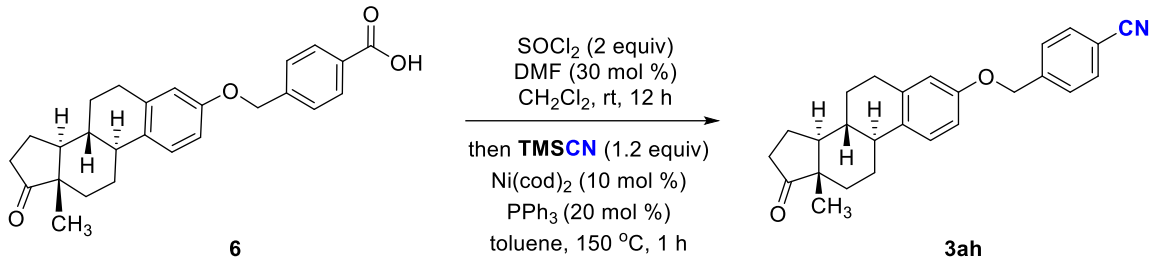
Synthesis of 4-((((8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)methyl)benzoic acid (6)[42]



5 **6**

Compound **6** was subjected to hydrolysis according to the reported method.[43] A solution of compound **5** (418 g, 1 mmol) and lithium hydroxide monohydrate (84 mg, 2 mmol) in tetrahydrofuran (2 mL) and water (2 mL) was refluxed at 100 °C. After 4 h, the solvent was evaporated, and concentrated HCl was added to the residue. The precipitate was filtrated, washed with water, dried under vacuum to give a white solid (291 mg, 82%). ^1H NMR (600 MHz, $(CD_3)_2SO$): δ 0.81 (s, 3H), 1.30-1.39 (m, 3H), 1.44-1.57 (m, 3H), 1.72-1.77 (m, 1H), 1.89-1.96 (m, 2H), 2.05 (dt, J = 18.5, 8.5 Hz, 1H), 2.14-2.18 (m, 1H), 2.29-3.35 (m, 1H), 2.43 (dd, J = 18.5, 8.5 Hz, 1H), 2.79-2.82 (m, 2H), 3.36 (brs, 1H), 5.14 (s, 2H), 6.72 (d, J = 2.8 Hz, 1H), 6.76 (dd, J = 8.6, 2.8 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $(CD_3)_2SO$): δ 13.6, 21.2, 25.5, 26.1, 29.2, 31.4, 35.4, 37.8, 43.5, 47.4, 49.6, 68.4, 112.3, 114.6, 126.4, 127.2, 129.5, 130.3, 132.2, 137.6, 142.4, 156.0, 167.2, 219.8. FT-IR (KBr): 2932, 2876, 1734, 1678, 1611, 1497, 1425, 1254, 1159, 1057, 1005, 860 cm^{-1}. Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98%. Found: C, 77.03; H, 6.80%.

4-((((8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a] phenanthren-3-yl)oxy)methyl)benzonitrile (3ah)

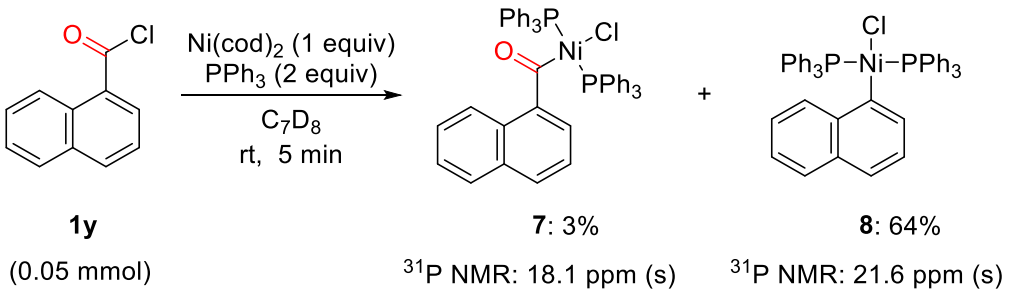


6 3ah

To the solution of anhydrous 1,2-dichloromethane (0.8 mL) and DMF (5 μL) of carboxylic acid **6** (80.9 mg, 0.2 mmol) in an oven-dried Schlenk tube containing a stirring bar, was added dropwise thionyl chloride (47.6 mg, 0.4 mmol, 2 equiv) using a syringe. The reaction mixture was stirred at room temperature for 12 h. The solvent and unreacted thionyl chloride were removed under reduced pressure. The resulting acyl chloride was used without additional purification. Then $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 10 mol %), PPh_3 (10.5 mg, 0.04 mmol, 20.0 mol %), toluene (1 mL), and TMSCN (23.4 mg, 0.24 mmol, 1.2 equiv) were successively added. The mixture was stirred at 150 ºC for 1 h. After cooling to room temperature, the crude product was purified by column chromatography on silica gel to afford the corresponding nitriles **3ah**.

White solid. Yield was 74% (57 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.40-1.65 (m, 6H), 1.94-1.97 (m, 1H), 1.99-2.08 (m, 2H), 2.15 (dt, J = 19.0, 9.0 Hz, 1H), 2.23-2.29 (m, 1H), 2.37-2.41 (m, 1H), 2.51 (dd, J = 19.0, 9.0 Hz, 1H), 2.88-2.91 (m, 2H), 5.14 (s, 2H), 6.71 (d, J = 3.0 Hz, 1H), 6.76 (dd, J = 8.4, 3.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 8.13 (dt, J = 8.4, 1.8 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 14.0, 21.7, 26.0, 26.6, 29.8, 31.7, 36.0, 38.4, 44.1, 48.1, 50.5, 68.9, 112.4, 115.0, 126.7, 127.3, 131.9, 132.7, 133.0, 138.2, 145.7, 156.3, 168.2, 221.1. FT-IR (KBr): 2991, 2926, 2378, 1734, 1606, 1219, 908, 793, 650 cm^{-1}. Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63%. Found: C, 81.10; H, 7.04; N, 3.58%.

2-4-2-4 Stoichiometric Reaction of $Ni(cod)_2$/2 PPh_3 with 1-Naphthoyl Chloride (1y)



An oven-dried 20 mL of Schlenk tube containing a stirring bar was charged with $Ni(cod)_2$ (13.7 mg, 0.05 mmol), PPh_3 (26.2 mg, 0.1 mmol) in C_7D_8 (0.4 mL) at room temperature. In a separate Schlenk tube, acyl chloride **1y** (9.5 mg, 0.05 mmol) was dissolved in C_7D_8 (0.2 mL) at room temperature. The $Ni(cod)_2/PPh_3$ solution was transferred to the solution of **1y** via a cannula. The resulting dark red solution was immediately subjected to the $^{31}P\{^1H\}$ NMR measurements.

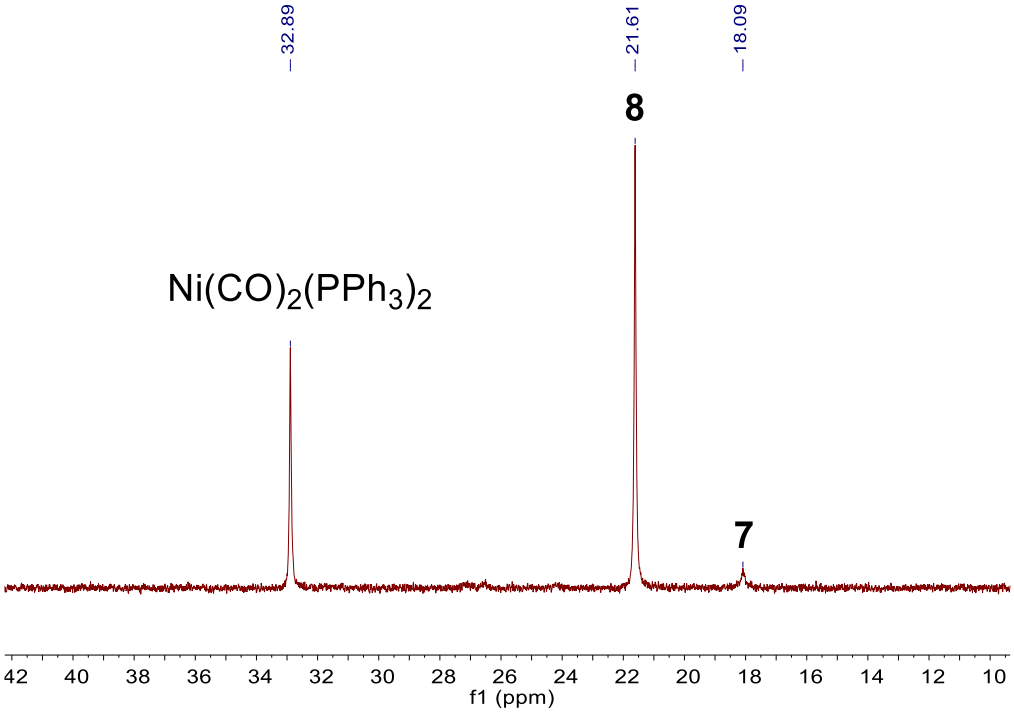
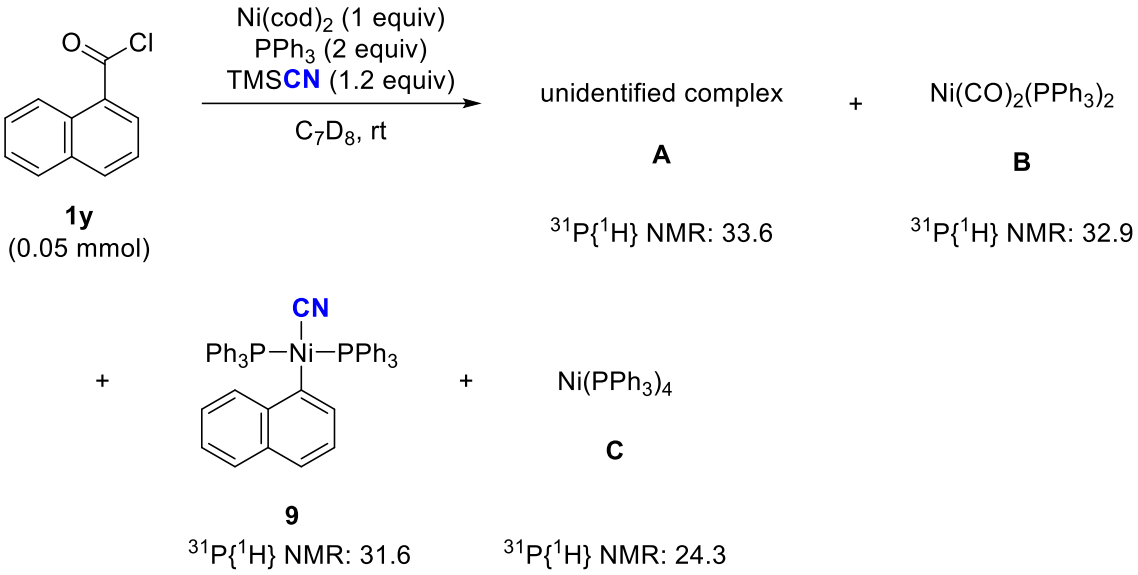


Figure 3. Stoichiometric reaction of 1-naphthoyl chloride with $Ni(cod)_2$ and PPh_3 at rt in C_7D_8 over 5 min

2-4-2-5 Reaction of 1y with $Ni(cod)_2$/ 2 PPh_3 in the Presence of TMSCN Characterization of Ni complexes. To an oven-dried 20 mL of Schlenk tube with a stirring bar, were added $Ni(cod)_2$ (13.8 mg, 0.05 mmol), PPh_3 (26.2 mg, 0.1 mmol), and

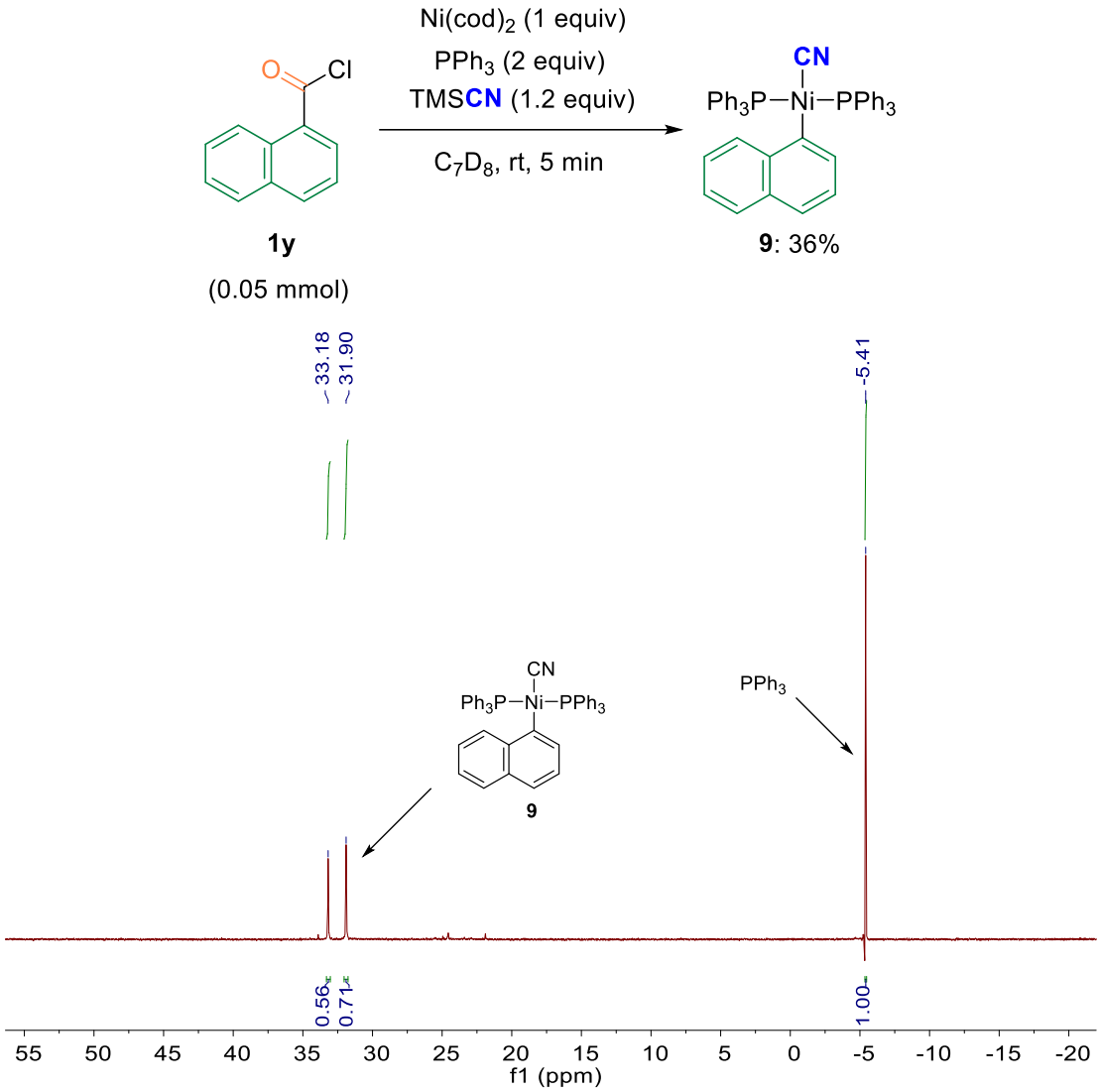
C_7D_8 (0.4 mL) under an argon atmosphere. In the other Schlenk tube, 1-naphthoyl chloride (**1y**) (9.5 mg, 0.05 mmol) and TMSCN (6.0 mg, 0.06 mmol, 1.2 equiv) were dissolved in C_7D_8 (0.2 mL). The $Ni(cod)_2/PPh_3$ solution was transferred to an NMR tube under Ar. After the solution of **1y** and TMSCN was added to the NMR tube, the reaction was immediately monitored with $^{31}P\{^1H\}$ NMR spectroscopy at room temperature.



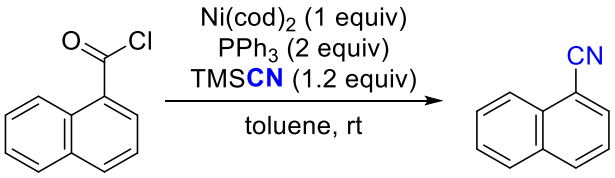
entry	time (min)	**A** (%)	**B** (%)	**9** (%)	**C** (%)
1	5	2	28	36	4
2	8	2	28	36	4
3	12	3	39	35	4
4	16	3	39	39	4
5	23	3	38	34	4
6	30	3	40	35	4
7	60	3	38	33	0
8	90	4	38	35	0

Determination of the $^{31}P\{^1H\}$ NMR yield. A sealed capillary containing a deuterium toluene solution of PPh_3 (13.1 mg, 0.05 mmol) was put into an oven dried NMR tube. The NMR tube was moved to a big Schlenk tube and vacuum, then argon refilled three times. To the NMR tube charged with $Ni(cod)_2$ (13.8 mg, 0.05 mmol), PPh_3 (26.2 mg, 0.1 mmol, 2 equiv), **3y** (7.7 mg, 0.05 mmol), TMSCN (8 μL, 0.06 mmol, 1.2 equiv) and

C_7D_8 (0.5 mL). The NMR tube was capped and heat up at measurement ^{31}P NMR at room temperature



Characterization of Reductive Elimination Product 3y. To an oven-dried 20 mL of Schlenk tube with a stirring bar, were added $Ni(cod)_2$ (13.8 mg, 0.05 mmol), PPh_3 (26.2 mg, 0.1 mmol), and toluene (0.4 mL) under an argon atmosphere. In the other Schlenk tube, 1-naphthoyl chloride (**1y**) (9.5 mg, 0.05 mmol), TMSCN (6.0 mg, 0.06 mmol, 1.2 equiv) and *n*-dodecane (8.5 mg, 0.05 mmol) was dissolved in toluene (0.2 mL). The $Ni(cod)_2/PPh_3$ solution was transferred into the solution containing **1y** and TMSCN via a cannula. The reaction was monitored by GC.

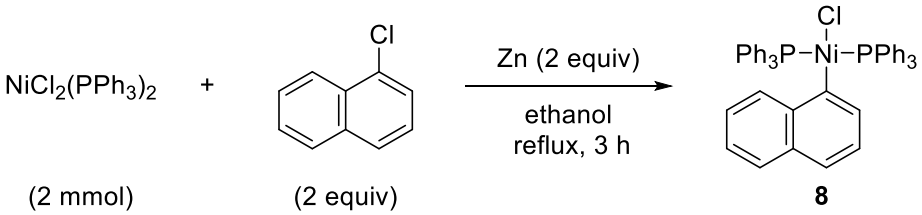


1y
(0.05 mmol)

3y

entry	time (h)	GC yield of **3y** (%)
1	0.08 (= 5 min)	47
2	0.5	58
3	1	60
4	3	60
5	6	60
6	12	60

2-4-2-6 Synthesis of *trans*-Ni(1-Np)Cl(PPh$_3$)$_2$ (8)



(2 mmol)

(2 equiv)

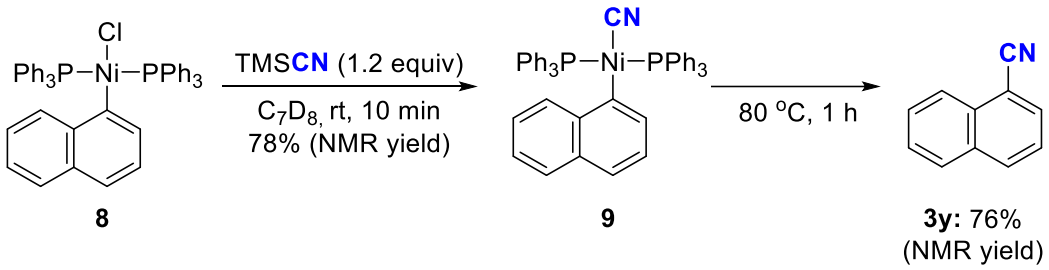
8

trans-Ni(1-Np)Cl(PPh$_3$)$_2$ (**8**) was prepared according to a modified literature procedure.[44] To the ethanol (12 mL) solution of NiCl$_2$(PPh$_3$)$_2$ (1.3 g, 2 mmol) in an oven-dried Schlenk tube with a stirring bar were added 1-chloronaphthalene (650 mg, 0.54 mL, 4 mmol), Zn dust (262 mg, 4 mmol). The reaction mixture was stirred under reflux for 3 h and allowed to cool to room temperature. The yellow solid in green solution was filtrated, washed with ethanol (20 mL), dissolved in hot 1,2-dichloroethane (10 mL), and filtered through a pad of Celite. The Celite was then washed again with hot 1,2-dichloroethane (20 mL). Evaporation of the combined filtrates and orange oil was washed with hexane (60 mL), which was kept at −32 °C overnight. The resulting orange solid was separated by filtration, washed with hexane (2 × 20 mL), and dried under vacuum to yield *trans*-Ni(1-Np)Cl(PPh$_3$)$_2$ (**8**) in 74% yield (1.1 g, 1.48 mmol). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 6.45 (s, 1H), 6.72 (d, J = 7.9 Hz, 1H), 6.95 (m, J = 7.7 Hz, 1H),

7.01-7.06 (m, 2H), 7.12-7.18 (m, J = 7.8 Hz, 13H), 7.25 (s, 6H), 7.40-7.53 (m, 12H), 9.14 (d, J = 8.1 Hz, 1H); $^{31}P\{^{1}H\}$ NMR (243 MHz, C_6D_6): δ 21.6.

2-4-2-7 Reaction of Complex 8 with TMSCN

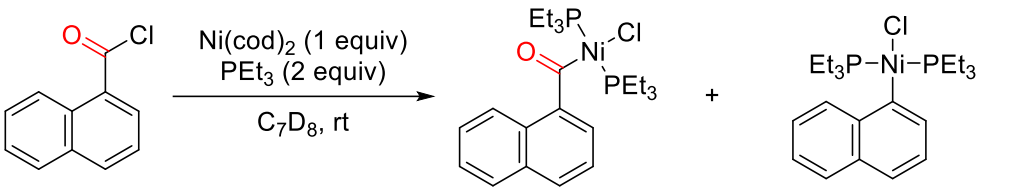
To an NMR tube charged with **8** (37.3 mg, 0.05 mmol), were added C_7D_8 (0.6 mL), TMSCN (6.0 mg, 0.06 mmol, 1.2 equiv), and *n*-dodecane (8.5 mg, 0.05 mmol) as an internal standard under an argon atmosphere. The mixture was monitored by the $^{31}P\{^{1}H\}$ NMR spectroscopy at room temperature, showing the formation of complex **9** in 78% yield. Next, the NMR tube was put in an oil bath at 80 ℃ for 1 h. The crude mixture was measured by GC, indicating the formation of **3y** in 76% GC yield.



2-4-2-8 Formation of Ni(1-NpCO)Cl(PEt_3)$_2$ (10) and Its Decarbonylation

Exp.1 Decarbonylation of **10** at Room Temperature

An oven-dried Schlenk tube with a stirring bar, were added Ni(cod)$_2$ (13.8 mg, 0.05 mmol), PEt_3 (11.8 mg, 0.1 mmol), and C_7D_8 (0.4 mL) under an argon atmosphere. In the other Schlenk tube, 1-naphthoyl chloride (**1y**) (9.5 mg, 0.05 mmol) was dissolved in C_7D_8 (0.2 mL). The Ni(cod)$_2$/PEt_3 solution was added to the solution of **1y** via a cannula. The resulting dark red solution was immediately transferred to the NMR tube under argon. The reaction was monitored with $^{31}P\{^{1}H\}$ NMR spectroscopy at room temperature.



1y (0.05 mmol)

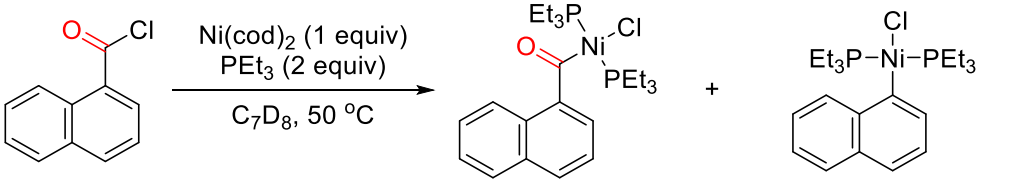
10 $^{31}P\{^{1}H\}$ NMR: 8.9 ppm

11 $^{31}P\{^{1}H\}$ NMR: 10.9 ppm

5 min	91	9
12 h	75	25

Exp.2 Decarbonylation of **10** at 50 °C

An oven-dried Schlenk tube with a stirring bar, were added $Ni(cod)_2$ (13.8 mg, 0.05 mmol), PEt_3 (11.8 mg, 0.1 mmol), and C_7D_8 (0.4 mL) under an argon atmosphere. In the other Schlenk tube, 1-naphthoyl chloride (**1y**) (9.5 mg, 0.05 mmol) was dissolved in C_7D_8 (0.2 mL). The $Ni(cod)_2/PEt_3$ solution was added to the solution of **1y** via a cannula. The resulting dark red solution was immediately transferred to the NMR tube under argon. The NMR tube was put in an oil bath heated up at 50 °C and monitored with $^{31}P\{^{1}H\}$ NMR spectroscopy.



1y (0.05 mmol)

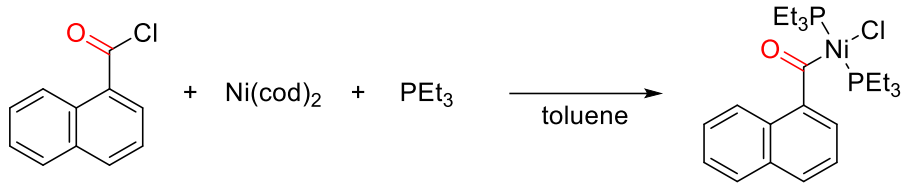
10 $^{31}P\{^{1}H\}$ NMR: 8.9 ppm

11 $^{31}P\{^{1}H\}$ NMR: 10.9 ppm

entry	time (h)	**10** (%)	**11** (%)
1	0.08 (= 5 min)	75	19
2	0.5 (= 30 min)	69	25
3	3	63	30
4	5	56	37
5	24	56	38

2-4-2-9 Synthesis of *trans*-Ni(1-NpCO)Cl(PEt_3)$_2$ (10)

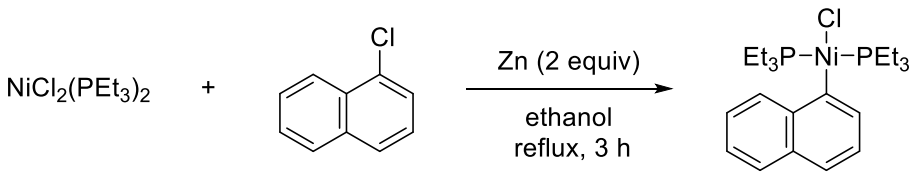
Oxidative Addition of **1y** to $Ni(cod)_2$/2 PEt_3



1y (0.2 mmol) (1 equiv) (2 equiv) **10**

An oven-dried Schlenk tube containing a stirring bar was charged with $Ni(cod)_2$ (55 mg, 0.2 mmol), PEt_3 (47.3 mg, 0.4 mmol), and toluene (0.4 mL) under an argon atmosphere. In the other Schlenk tube, 1-naphthoyl chloride (**1y**) (38.1 mg, 0.2 mmol) was dissolved in toluene (0.2 mL). The $Ni(cod)_2$/PEt_3 solution was transferred to the solution of **1y** via a cannula. The resulting dark red solution was stirred for 5 min and transferred to an NMR tube. Anhydrous hexane (1 mL) was added to the NMR tube, the tube was sealed and placed into a –20 °C freezer overnight, red crystals of **10** were obtained in 45% yield (44 mg, 0.09 mmol). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 1.12 (dt, $J_{P\text{-}H}$ = 15.0 Hz, J = 7.2 Hz, 18H), 1.51 (d, $J_{P\text{-}H}$ = 114 Hz, 12H), 7.49 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 9.27 (brs, 1H), 9.97 (brs, 1H); ^{13}C{^{1}H} NMR (151 MHz, CD_2Cl_2): δ 7.6, 14.0 (apparent triplet due to virtual coupling, $^{1+3}J_{P\text{-}C}$ = 13 Hz), 123.2, 124.6, 125.5, 126.0, 127.7, 127.9, 128.3, 131.8, 133.2, 133.5, 136.3 (t, $J_{P\text{-}C}$ = 5 Hz); ^{31}P{^{1}H} NMR (243 MHz, CD_2Cl_2): δ 8.7. FT-IR (KBr): 2964, 2931, 2904, 2873, 1634, 1601, 1504, 1454, 1416,1375, 1339, 1254, 1196, 1155, 885, 820, 787, 762, 745, 721, 698, 678, 658 cm^{-1}. Anal. Calcd for $C_{23}H_{37}ClOP_2Ni$: C, 56.88; H, 7.68%. Found: C, 56.85; H, 7.81%.

2-4-2-10 Synthesis of *trans*-Ni(1-Np)Cl(PEt_3)$_2$ (11)

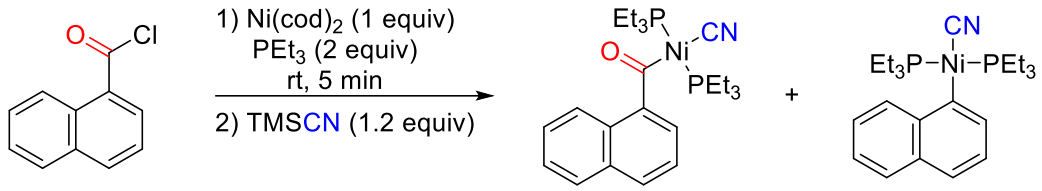


(2 mmol) (2 equiv) **11**

trans-Ni(1-Np)Cl(PEt_3)$_2$ (**10**) was prepared according to a modified literature procedure.[18] To the ethanol (12 mL) solution of $NiCl_2(PEt_3)_2$ (732 mg, 2 mmol), 1-chloronaphthalene (650 mg, 0.54 mL, 4 mmol) in an oven dried Schlenk tube with a stirring bar, was added Zn dust (262 mg, 4 mmol). The reaction mixture was stirred under reflux for 3 h and allowed to cool to room temperature. The yellow solid was separated, washed with ethanol (20 mL), dissolved in hot 1,2-dichloroethane (10 mL), and filtered through a pad of Celite. The Celite was then washed again with additional 1,2-dichloroethane (20 mL). Evaporation of the combined filtrates and the oily orange solid was washed with hexane (60 mL), which was kept at −32 °C overnight. The resulting orange solid was separated by filtration, washed with hexane (2 × 20 mL), and dried under vacuum to yield *trans*-Ni(1-Np)Cl(PEt_3)$_2$ (**11**) in 50% yield (458 mg, 1 mmol). ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 1.06 (dt, $J_{P\text{-}H}$ = 15.6 Hz, J = 7.2 Hz,18H), 1.24 (brd, $J_{P\text{-}H}$ = 72.6 Hz, 12H), 7.06 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.52 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 9.23 (d, J = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $(CD_3)_2CO$): δ 8.3, 14.3 (apparent triplet due to virtual coupling, $^{1+3}J_{P\text{-}C}$ = 13 Hz), 121.9, 123.9, 125.1, 125.6, 129.0, 133.8, 133.9, 134.3, 140.9, 157.5 (t, $J_{P\text{-}C}$ = 34.2 Hz); ^{31}P{^{1}H} NMR (243 MHz, C_6D_6) δ 10.9. FT-IR (KBr): 3040, 2963, 2930, 2909, 2872, 1541, 1491, 1452, 1412, 1369, 1240, 1032, 1009, 1001, 953, 789, 760, 721 cm^{-1}. Anal. Calcd for $C_{22}H_{37}ClP_2Ni$: C, 57.74; H, 8.15%. Found: C, 57.35; H, 8.40%.

2-4-2-11 Reaction of 1y with Ni(cod)$_2$/ 2 PEt_3 in the Presence of TMSCN

An oven-dried Schlenk tube with a stirring bar, were added Ni(cod)$_2$ (13.8 mg, 0.05 mmol), PEt_3 (11.8 mg, 0.1 mmol), and C_7D_8 (0.4 mL) under an argon atmosphere. In the other Schlenk tube, 1-naphthoyl chloride (**1y**) (9.5 mg, 0.05 mmol) was dissolved in C_7D_8 (0.2 mL). The Ni(cod)$_2$/PEt_3 solution was added to the solution of **1y** via a cannula and stirred at room temperature for 5 min, TMSCN (6.0 mg, 0.06 mmol, 1.2 equiv) was added to the mixture. This orange solution was immediately transferred to the NMR tube under Ar. The reaction was monitored with ^{31}P{^{1}H} NMR spectroscopy at room temperature.



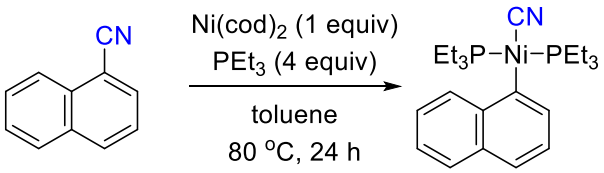
1y
(0.05 mmol)

12
$^{31}P\{^{1}H\}$ NMR: 15.1 ppm

13
$^{31}P\{^{1}H\}$ NMR: 18.6 ppm

entry	time (min)	**12** (%)	**13** (%)
1	2	66	11
2	7	56	11
3	30	41	12
4	62	31	16
5	92	27	22
6	135	25	25
7	150	21	26
8	210	0	27

2-4-2-12 Synthesis of *trans*-Ni(1-Np)CN(PEt$_3$)$_2$ (13) by Oxidative Addition of 3y to Ni(0) via C−CN Bond Cleavage

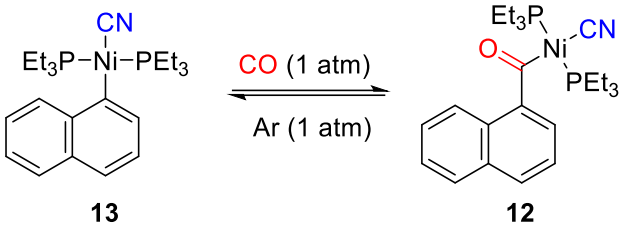


3y **13**

To the toluene (1 mL) solution of Ni(cod)$_2$ (200 mg, 0.72 mmol) in an oven-dried Schlenk tube with a stirring bar, was added PEt$_3$ (340 mg, 2.88 mmol, 4 equiv) under argon atmosphere. After the reaction mixture was stirred for 1 min, **3y** (110.2 mg, 0.72 mmol) was added to the reaction mixture, which was stirred at 80 °C for 24 h and allowed to cool to room temperature. The reaction mixture was filtered through a pad of Celite. The Celite was then washed with 1,2-dichloroethane (20 mL). Evaporation of the filtrates and a crude product was washed with hexane (20 mL). Yellow precipitates were formed and separated through a membrane filter. The yellow solid was washed with *n*-hexane (2 × 20 mL) and dried under vacuum to give *trans*-Ni(1-Np)CN(PEt$_3$)$_2$ (**13**) in

72% yield (232.9 mg, 0.52 mmol). Single crystals of complex **13** were obtained by diffusion method of the CH_2Cl_2 solution containing **13** with hexane at room temperature. ^{1}H NMR (600 MHz, CD_2Cl_2): δ 1.06 (dt, $J_{P\text{-}H}$ = 15.6 Hz, J = 7.8 Hz,18H), 1.37 (dm, $J_{P\text{-}H}$ = 52.2 Hz, 12H), 7.13 (t, J = 7.4 Hz, 1H), 7.27-7.41 (m, 4H), 7.65 (d, J = 7.2 Hz,, 1H), 8.49 (d, J = 7.2 Hz,, 1H); ^{13}C{^{1}H} NMR (151 MHz, CD_2Cl_2): δ 8.0, 15.4 (apparent triplet due to virtual coupling, $^{1+3}J_{P\text{-}C}$ = 14 Hz), 121.4 (t, $J_{P\text{-}C}$ = 3.0 Hz), 123.2, 124.6, 124.8 (t, $J_{P\text{-}C}$ = 2.8 Hz), 128.2, 132.7, 132.8 (t, $J_{P\text{-}C}$ = 4.7 Hz), 133.3 (t, $J_{P\text{-}C}$ = 2.3 Hz), 140.7 (d, $J_{P\text{-}C}$ = 2.3 Hz), 143.0 (t, $J_{P\text{-}C}$ = 26.4 Hz), 162.6 (t, $J_{P\text{-}C}$ = 30.4 Hz); ^{31}P{^{1}H} NMR (243 MHz, CD_2Cl_2): δ 18.4. FT-IR (KBr): 3044, 2963, 2926, 2870, 2360, 2093, 1541, 1493, 1452, 1418, 1369, 1258, 1038, 955, 799, 768, 725, 637 cm^{-1}. Anal. Calcd for $C_{23}H_{37}NP_2Ni$: C, 61.64; H, 8.32; N, 3.13%. Found: C, 61.62; H, 8.61; N, 3.05%.

2-4-2-13 Interconversion between 12 and 13 is Reversible



13 **12**

An oven-dried Schlenk tube charged with **13** (92 mg, 0.2 mmol) in C_7D_8 (0.6 mL) was evacuated and refilled with CO from a balloon three times. After the reaction mixture was stirred at room temperature for 3 h, the solution was transferred to an NMR tube to measure the ^{31}P{^{1}H} NMR spectroscopy. The ^{31}P{^{1}H} NMR spectrum showed the formation of **12** in 41% yield, along with complex **13** unreacted in 36% yield. On the other hand, after 3 h under an argon atmosphere in place of CO, the 73% yield of **13** was observed, indicating that interconversion between **12** and **13** is reversible.

2-4-3 Crystallographic Data of Complexes 10 and 13

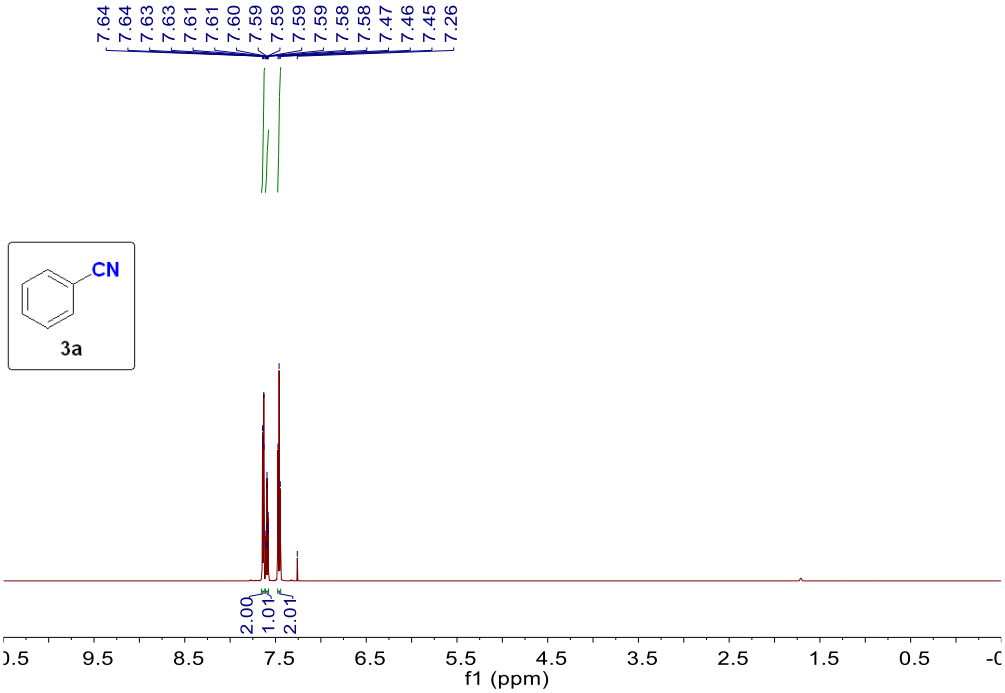
Table 2-4. Crystal Data and Structure Refinement for Complex **10**

Empirical formula	$C_{23}H_{37}ClNiOP_2$	
Formula weight	485.63	
Temperature	153(2) K	
Wavelength	0.71075 Å	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 12.148(4) Å	= 90°.
	b = 14.698(5) Å	= 89.854(5)°.
	c = 13.823(5) Å	= 90°.
Volume	2468.1(15) $Å^3$	
Z	4	
Density (calculated)	1.307 Mg/m^3	
Absorption coefficient	1.035 mm^{-1}	
F(000)	1032	
Crystal size	0.14 x 0.13 x 0.03 mm^3	
Theta range for data collection	2.02 to 27.50°.	
Index ranges	-15<=h<=11, -17<=k<=18, -17<=l<=17	
Reflections collected	20488	
Independent reflections	5630 [R(int) = 0.0317]	
Completeness to theta = 27.50°	99.5 %	
Max. and min. transmission	0.9696 and 0.8686	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5630 / 30 / 249	
Goodness-of-fit on F^2	1.109	
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.0855	
R indices (all data)	R1 = 0.0490, wR2 = 0.0952	
Largest diff. peak and hole	0.752 and -0.534 $e.Å^{-3}$	

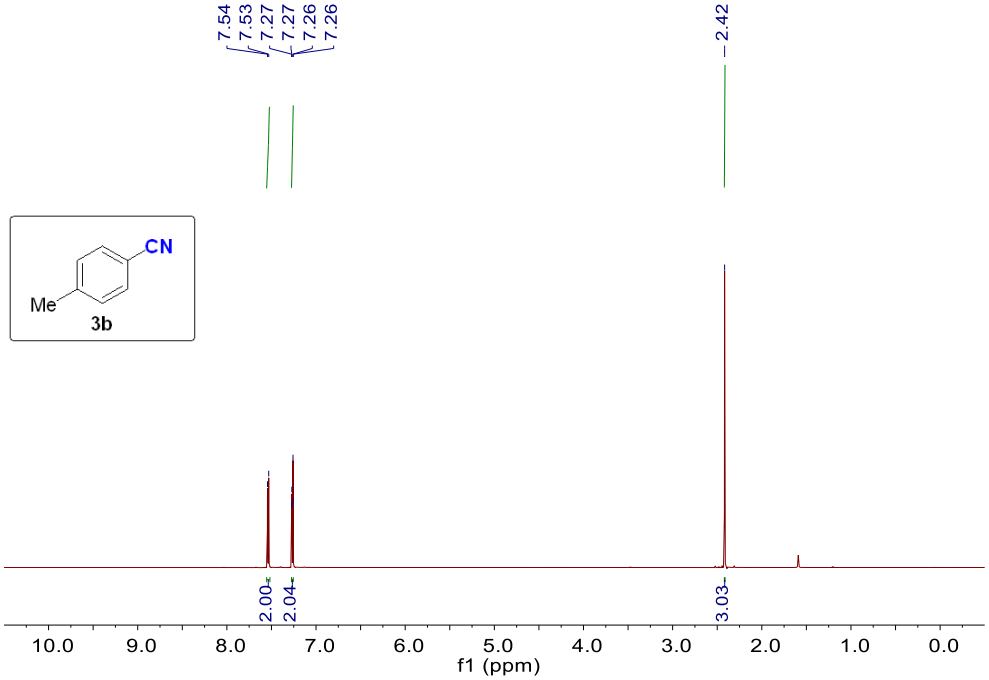
Table 2-5. Crystal Data and Structure Refinement for Complex **13**

Empirical formula	$C_{23}H_{37}NNiP_2$	
Formula weight	448.19	
Temperature	153(2) K	
Wavelength	0.71075 Å	
Crystal system	orthorhombic	
Space group	*Pna*2_1	
Unit cell dimensions	a = 18.336(4) Å	= 90°.
	b = 10.341(2) Å	= 90°.
	c = 12.785(3) Å	= 90°.
Volume	2424.2(9) $Å^3$	
Z	4	
Density (calculated)	1.228 Mg/m^3	
Absorption coefficient	0.940 mm^{-1}	
F(000)	960	
Crystal size	0.22 x 0.21 x 0.18 mm^3	
Theta range for data collection	2.26 to 26.00°.	
Index ranges	-22<=h<=22, -12<=k<=12, -15<=l<=15	
Reflections collected	17007	
Independent reflections	4640 [R(int) = 0.0257]	
Completeness to theta = 26.00°	99.1 %	
Max. and min. transmission	0.8490 and 0.8199	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4640 / 133 / 235	
Goodness-of-fit on F^2	1.077	
Final R indices [I>2sigma(I)]	R1 = 0.0917, wR2 = 0.2381	
R indices (all data)	R1 = 0.1064, wR2 = 0.2528	
Absolute structure parameter	0.47(5)	
Largest diff. peak and hole	2.298 and -1.513 e.$Å^{-3}$	

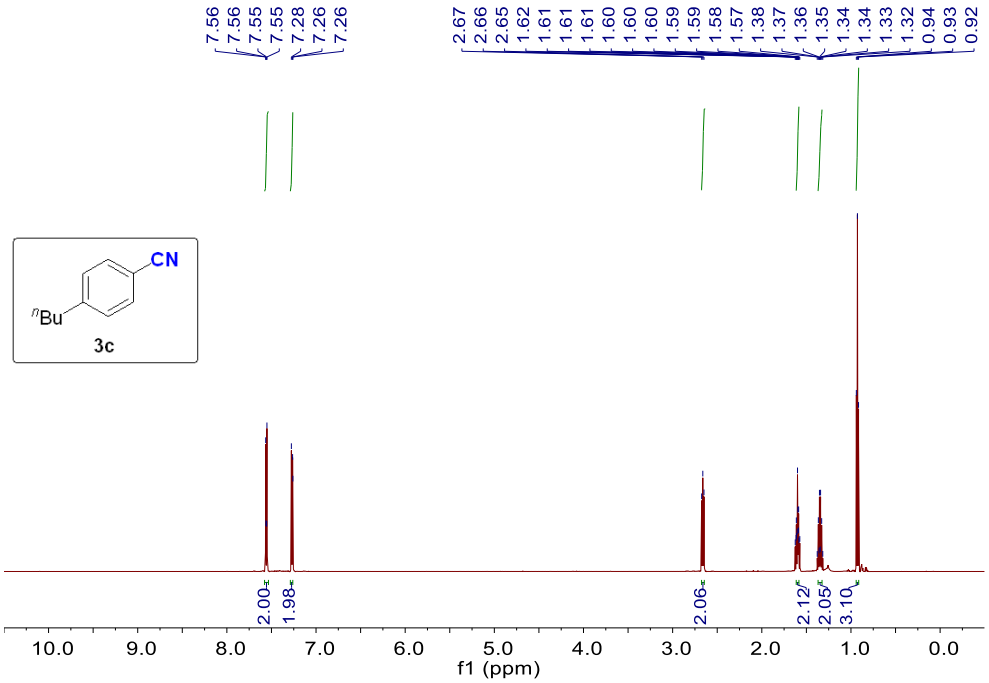
2-4-4 Copies of ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR Charts



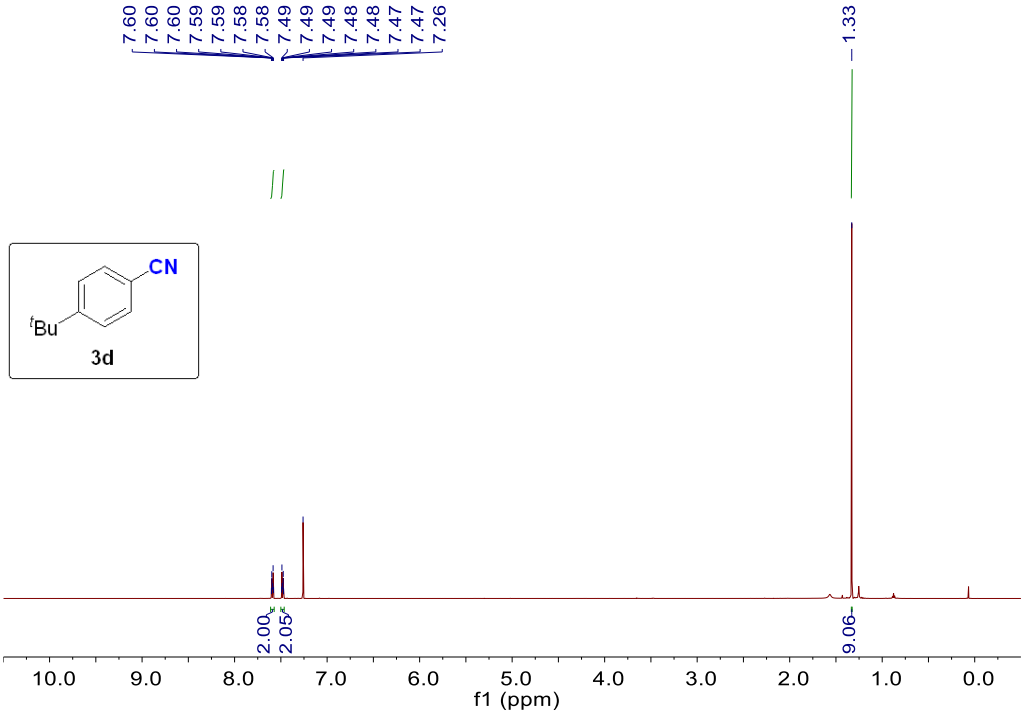
^{1}H NMR (600 MHz) spectrum of **3a** ($CDCl_3$, rt).



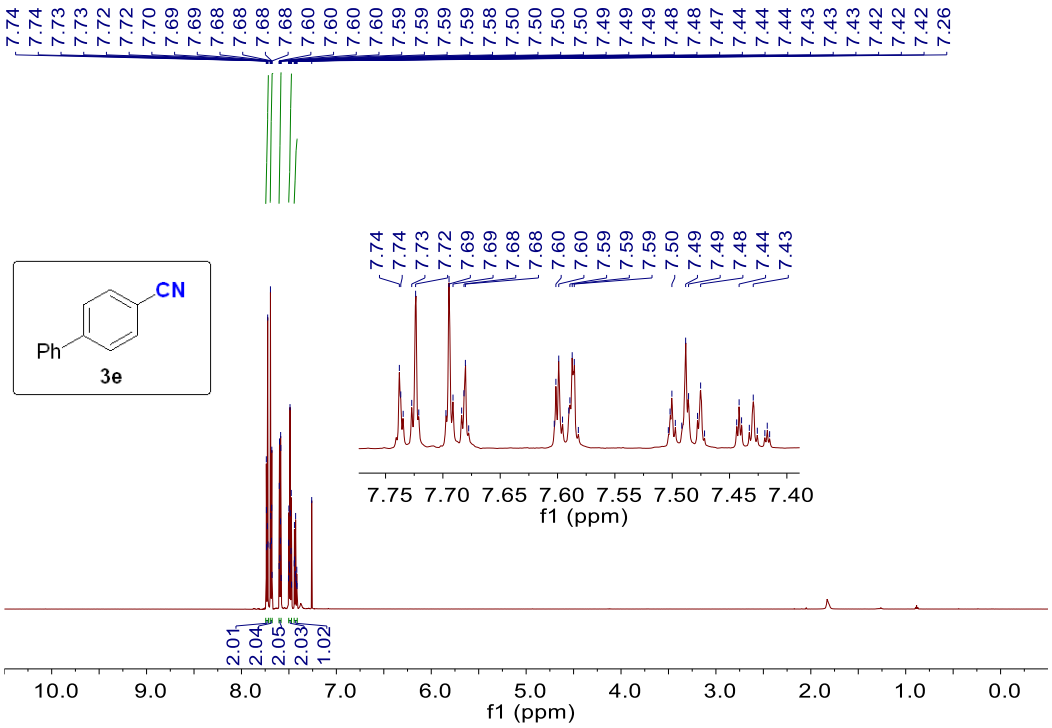
^{1}H NMR (600 MHz) spectrum of **3b** ($CDCl_3$, rt).



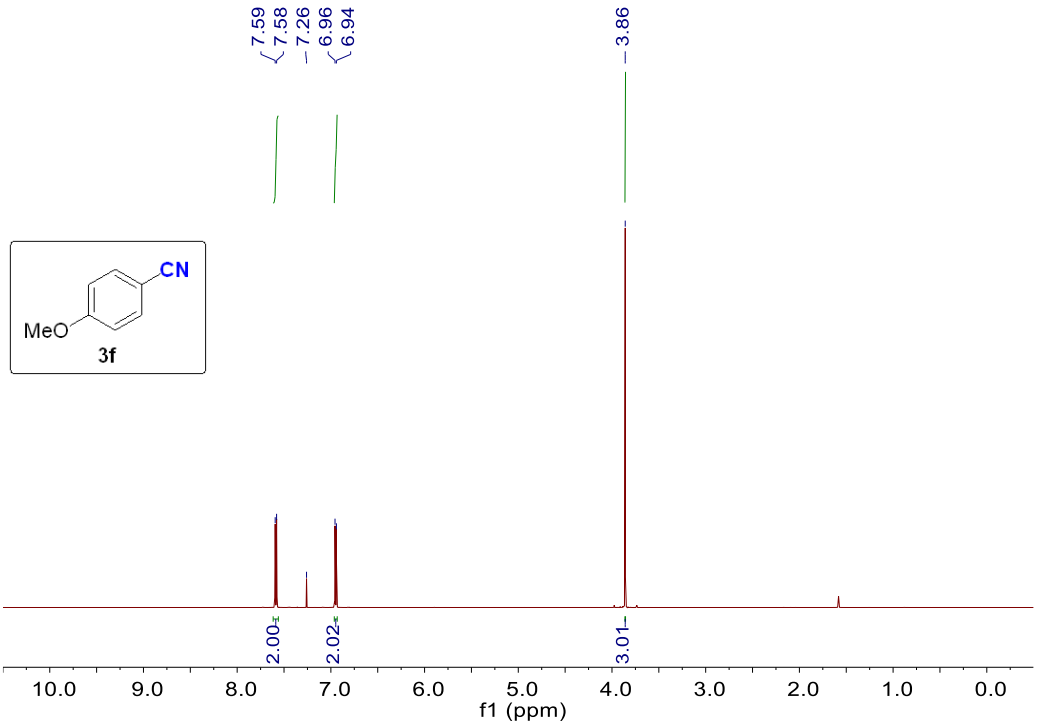
^{1}H NMR (600 MHz) spectrum of **3c** ($CDCl_3$, rt).



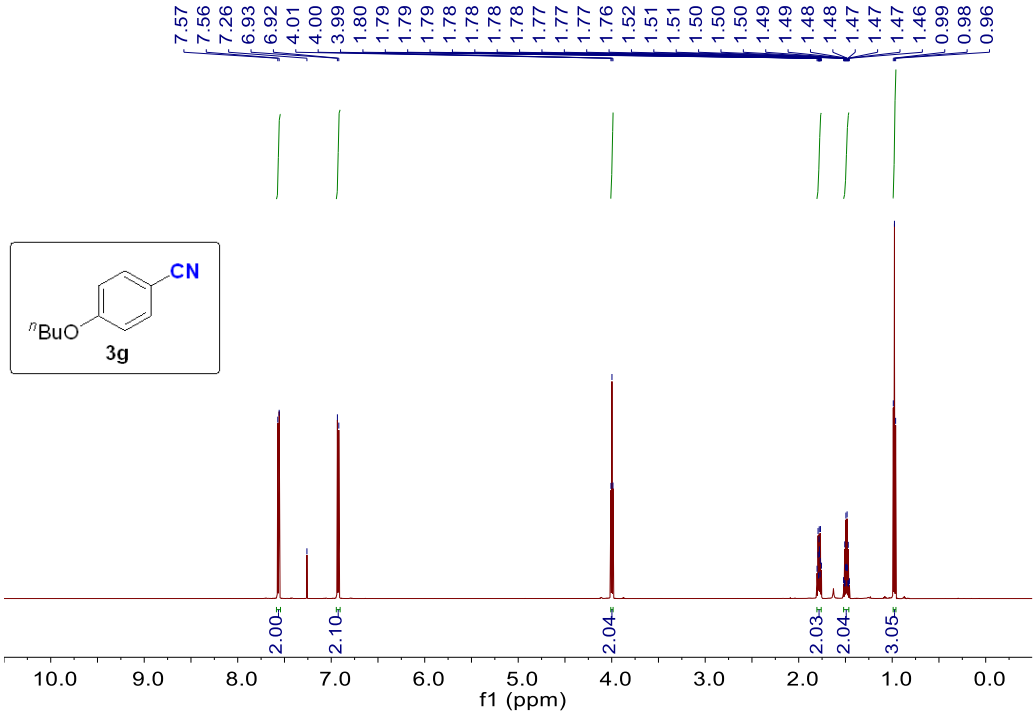
^{1}H NMR (600 MHz) spectrum of **3d** ($CDCl_3$, rt).



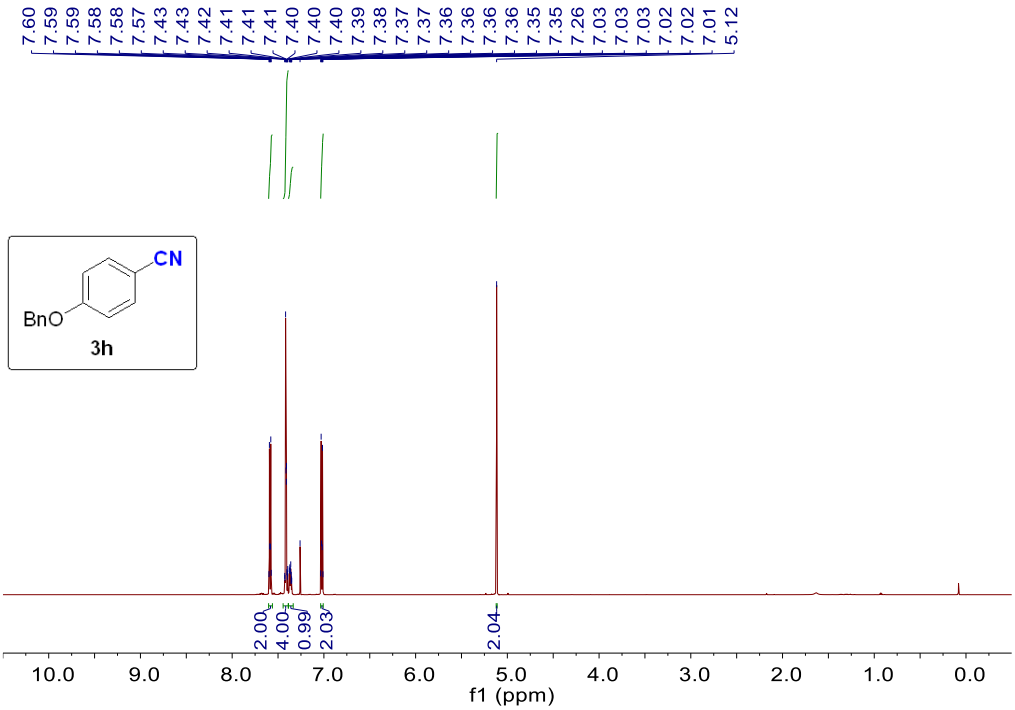
^{1}H NMR (600 MHz) spectrum of **3e** ($CDCl_3$, rt).



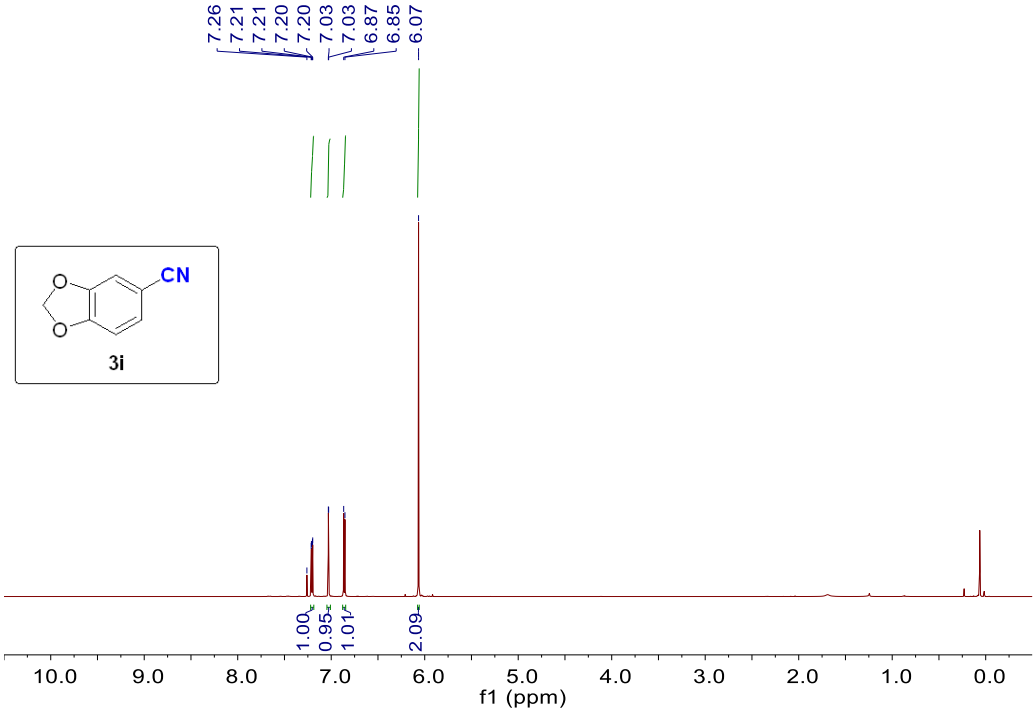
^{1}H NMR (600 MHz) spectrum of **3f** ($CDCl_3$, rt).



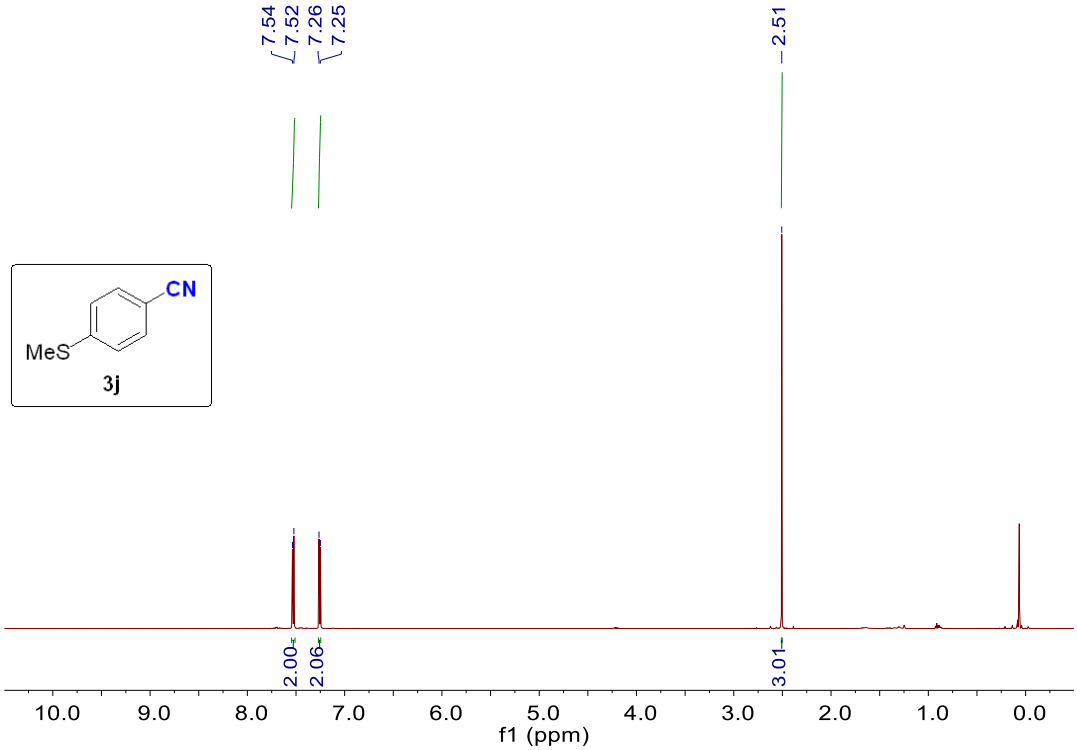
^{1}H NMR (600 MHz) spectrum of **3g** ($CDCl_3$, rt).



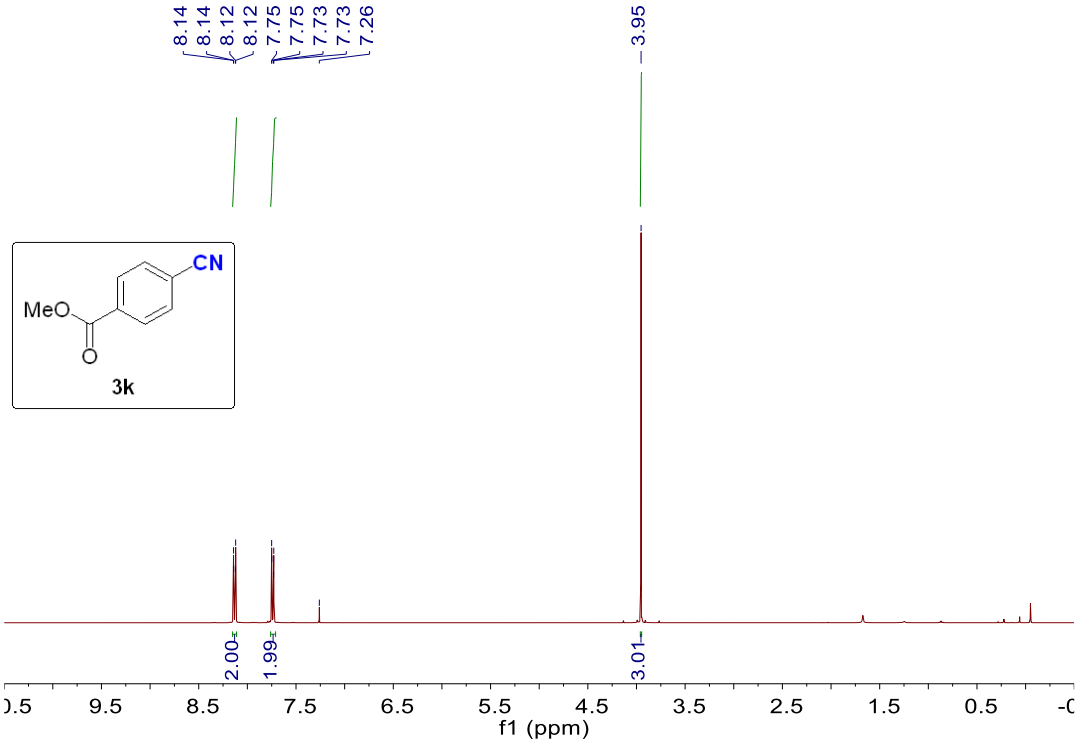
^{1}H NMR (600 MHz) spectrum of **3h** ($CDCl_3$, rt).



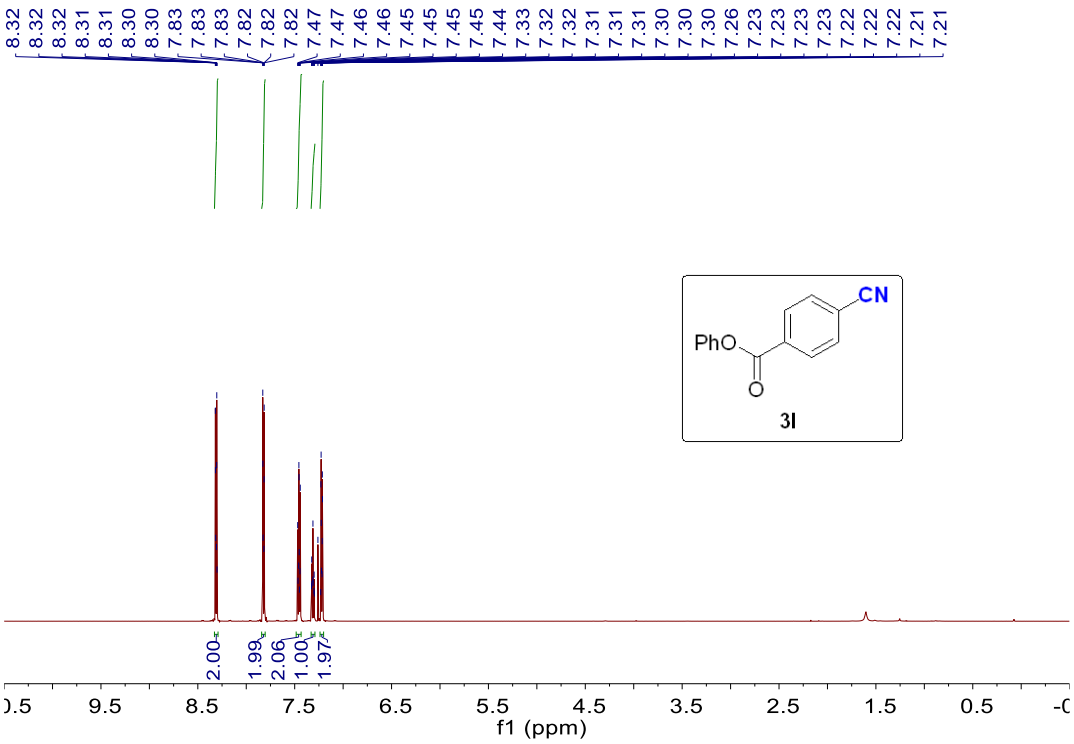
^{1}H NMR (600 MHz) spectrum of **3i** ($CDCl_3$, rt).



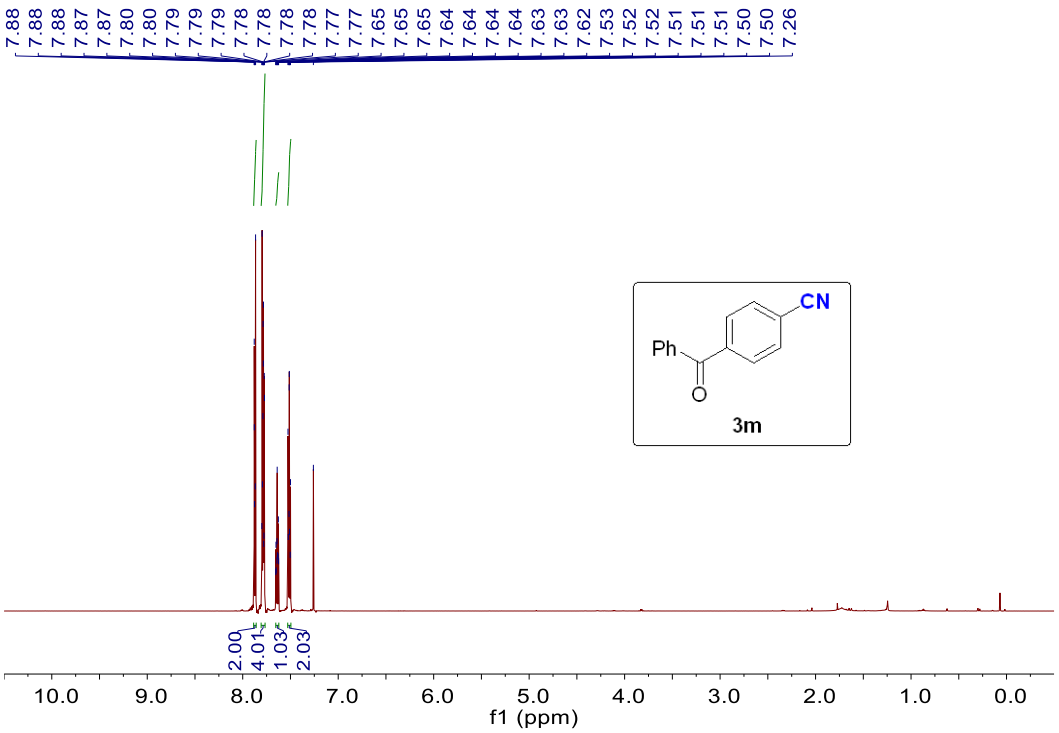
^{1}H NMR (600 MHz) spectrum of **3j** ($CDCl_3$, rt).



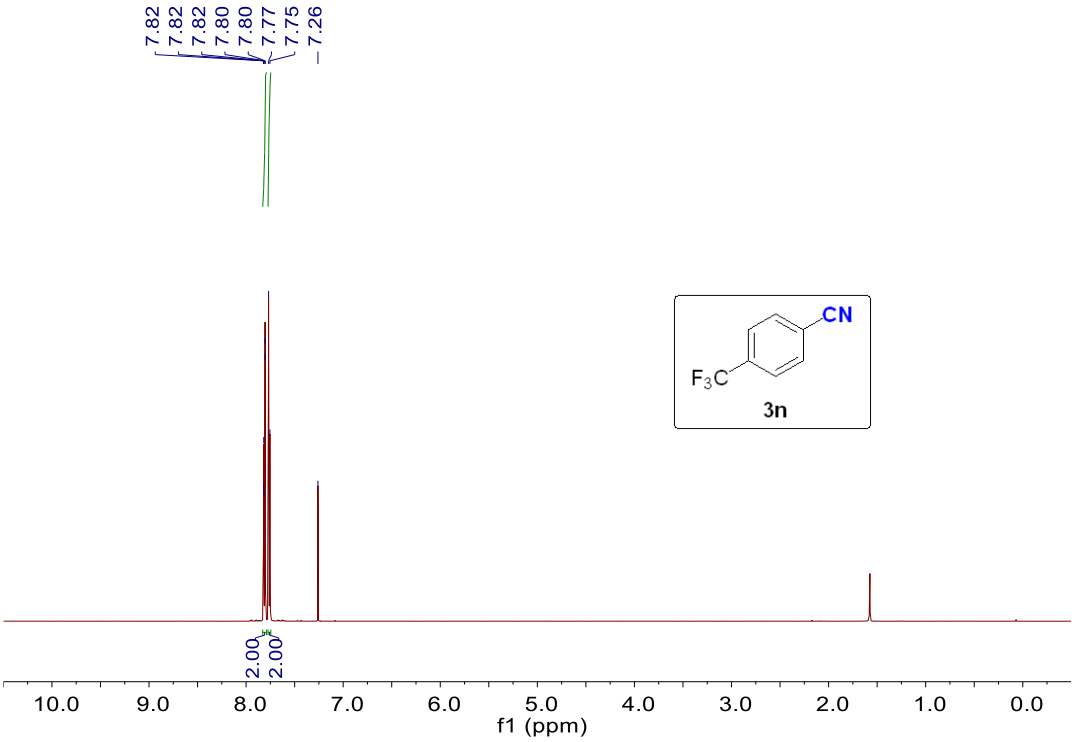
^{1}H NMR (400 MHz) spectrum of **3k** ($CDCl_3$, rt).



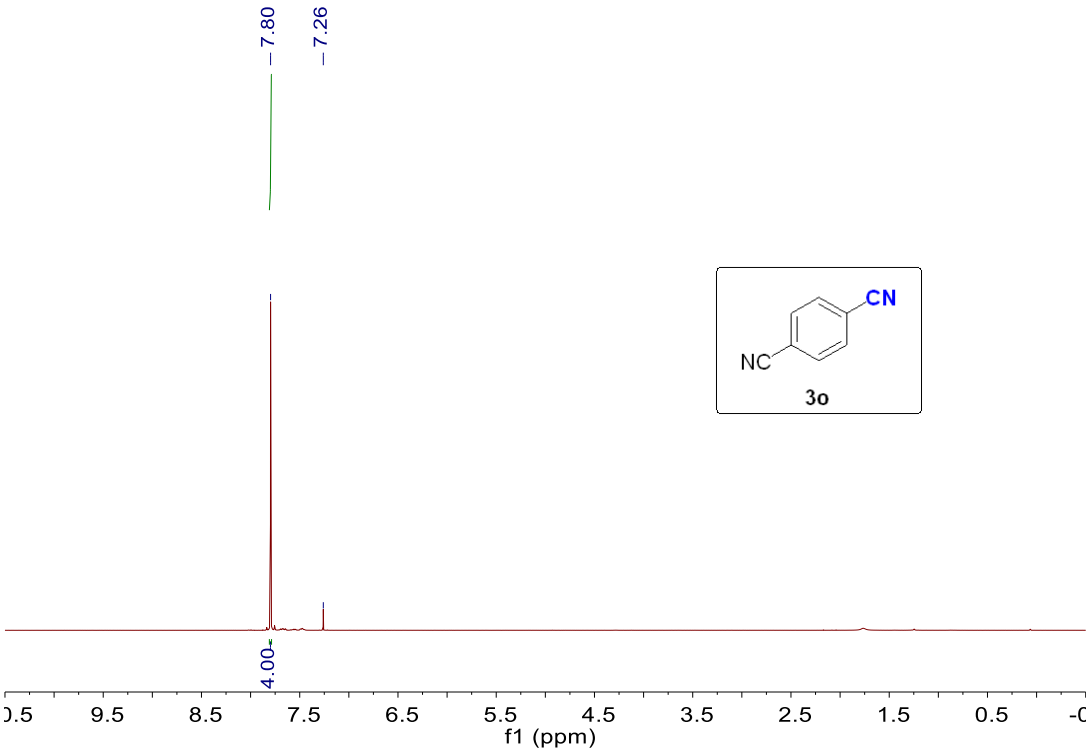
^{1}H NMR (600 MHz) spectrum of **3l** ($CDCl_3$, rt).



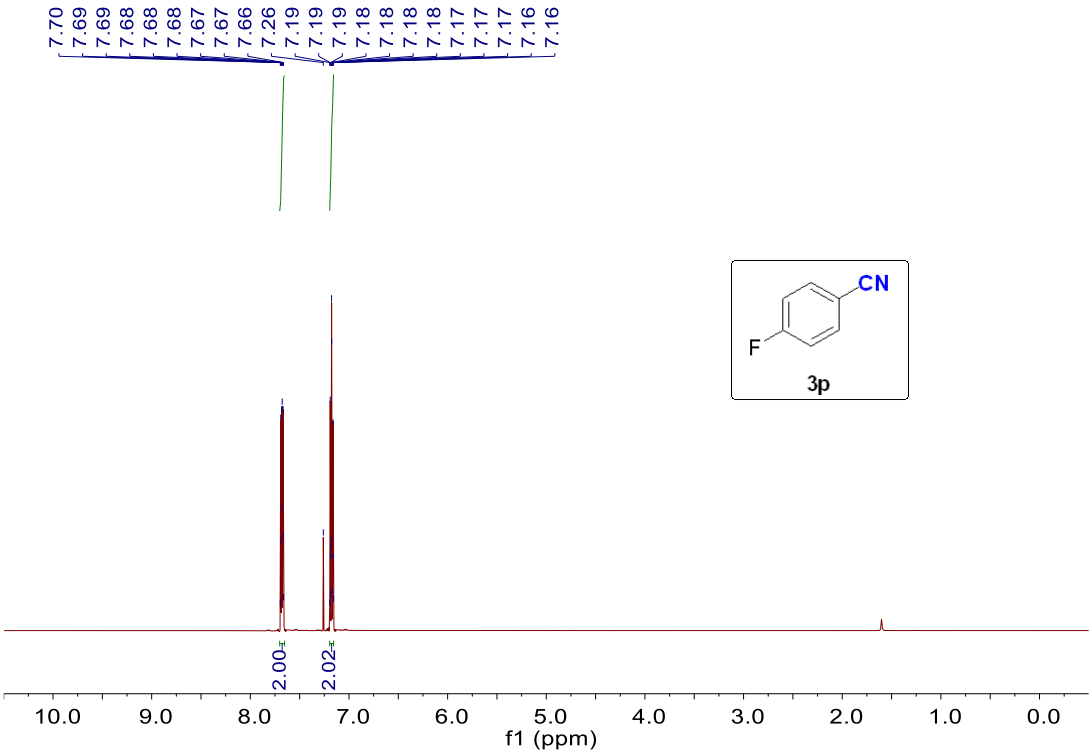
^{1}H NMR (600 MHz) spectrum of **3m** ($CDCl_3$, rt).



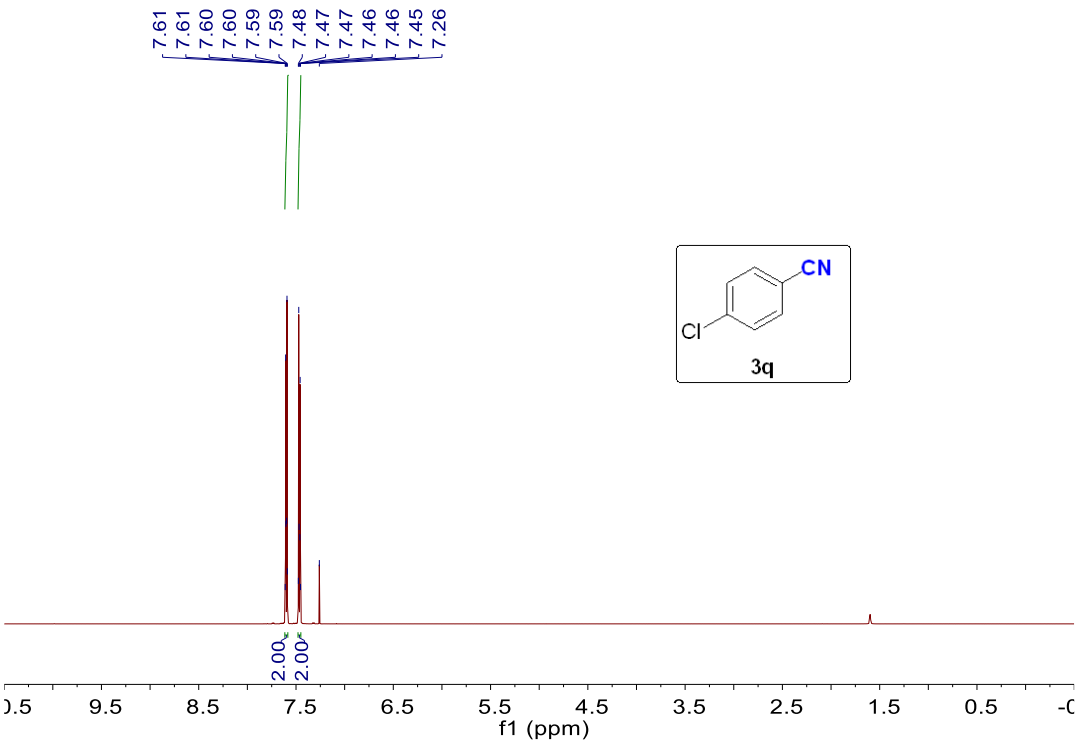
^{1}H NMR (600 MHz) spectrum of **3n** ($CDCl_3$, rt).



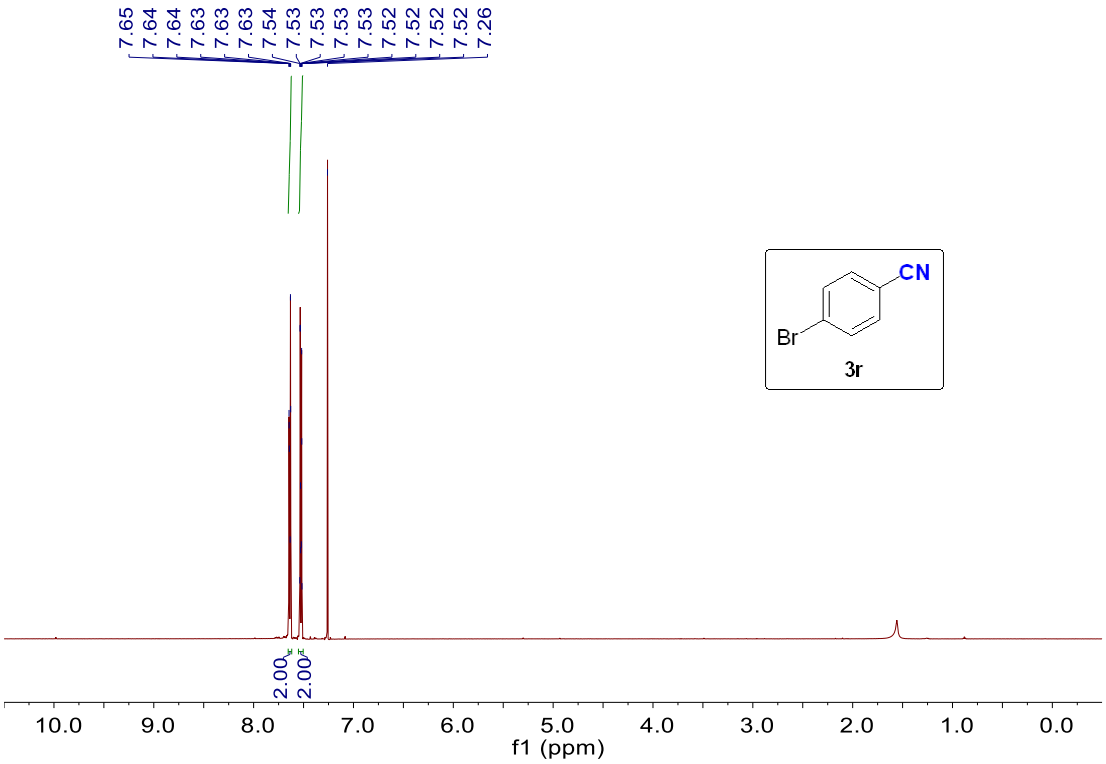
^{1}H NMR (400 MHz) spectrum of **3o** ($CDCl_3$, rt).



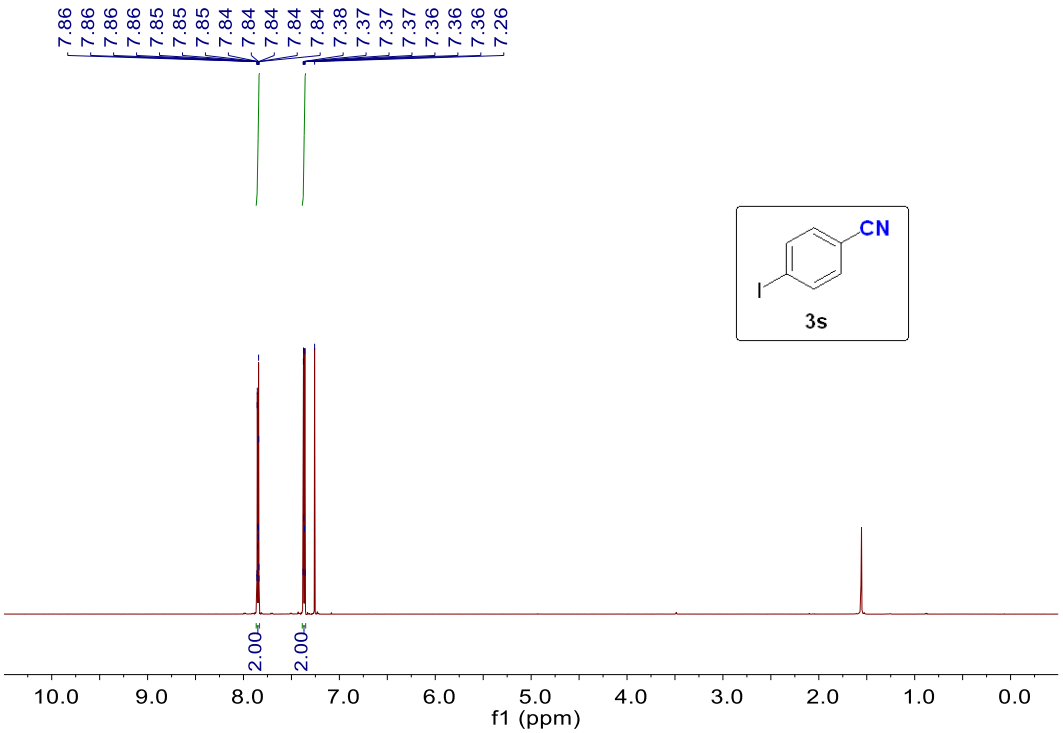
^{1}H NMR (600 MHz) spectrum of **3p** ($CDCl_3$, rt).



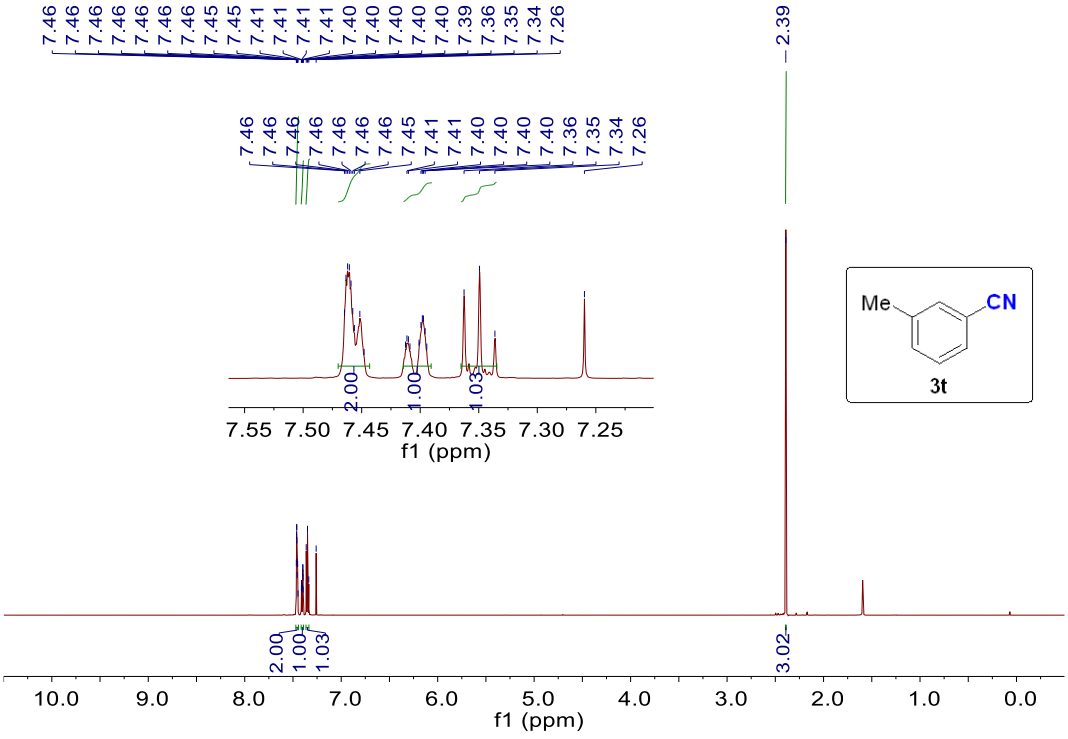
^{1}H NMR (600 MHz) spectrum of **3q** ($CDCl_3$, rt).



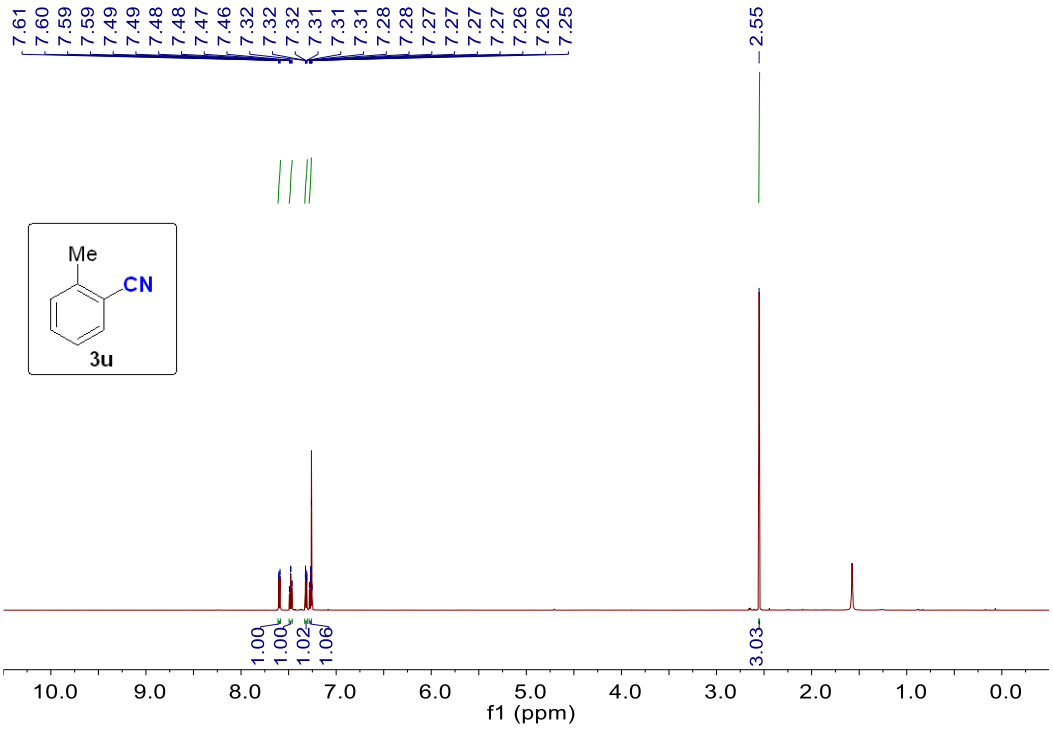
^{1}H NMR (600 MHz) spectrum of **3r** ($CDCl_3$, rt).



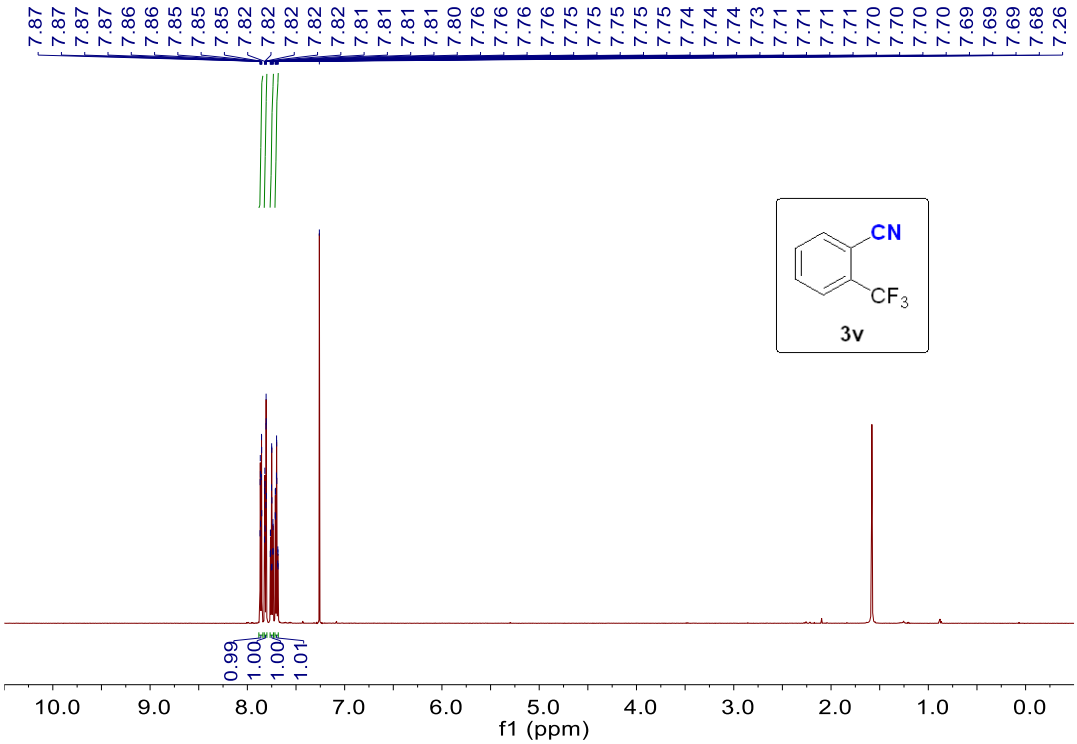
^{1}H NMR (600 MHz) spectrum of **3s** ($CDCl_3$, rt).



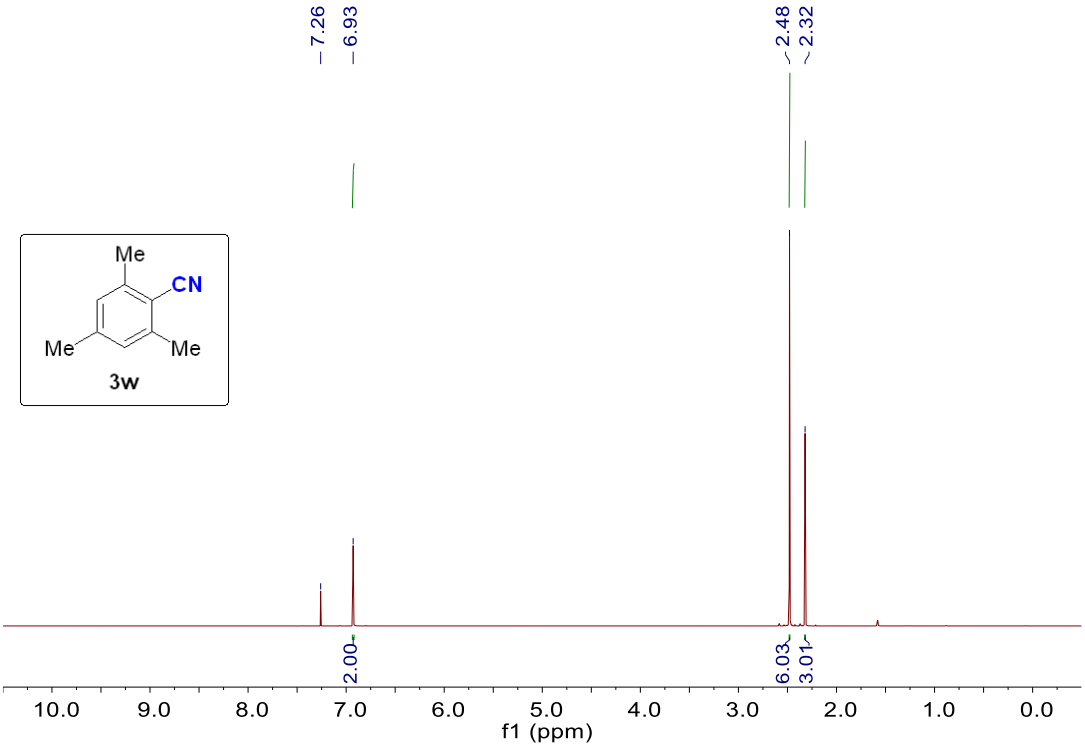
^{1}H NMR (600 MHz) spectrum of **3t** ($CDCl_3$, rt).



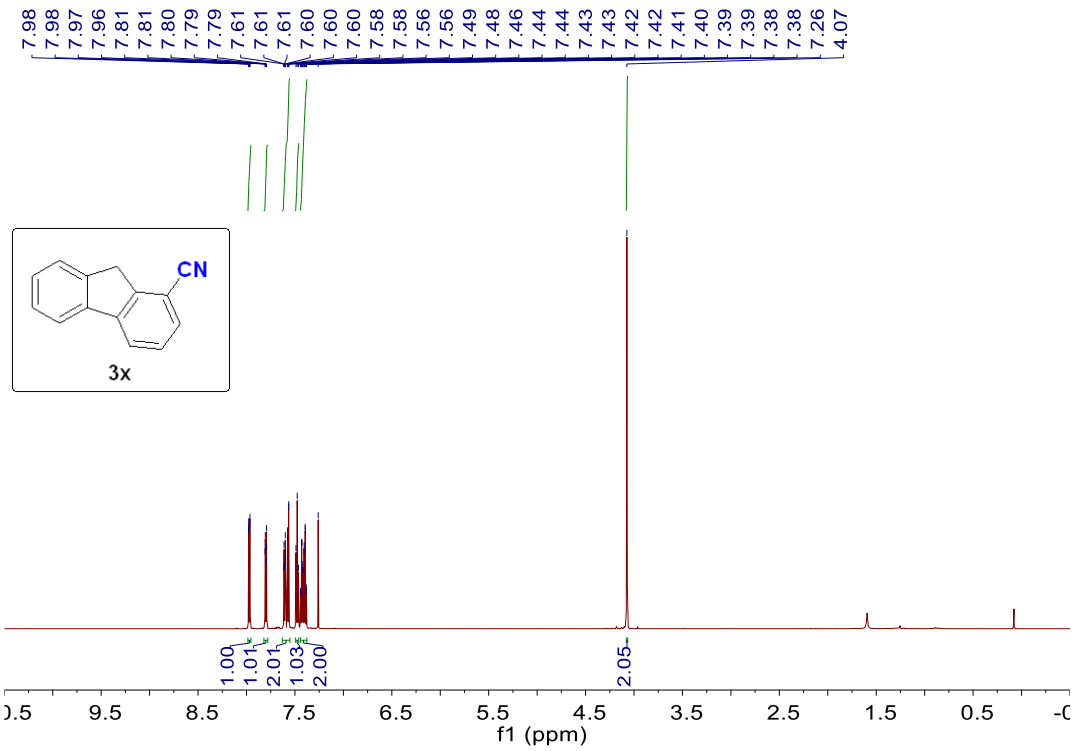
^{1}H NMR (600 MHz) spectrum of **3u** ($CDCl_3$, rt).



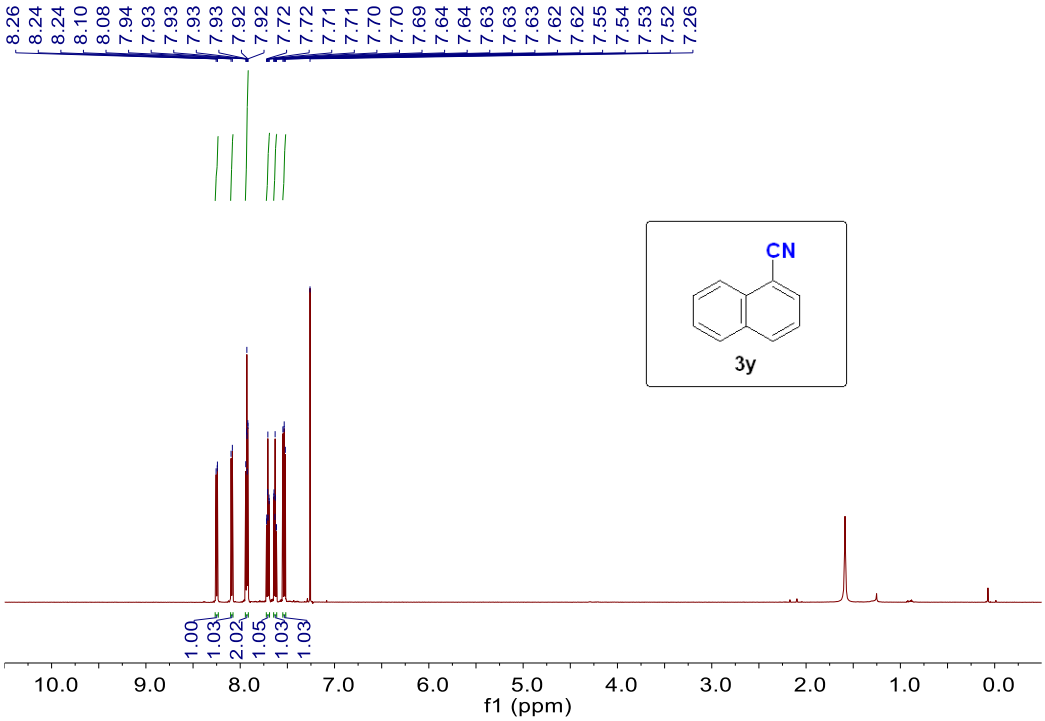
^{1}H NMR (600 MHz) spectrum of **3v** ($CDCl_3$, rt).



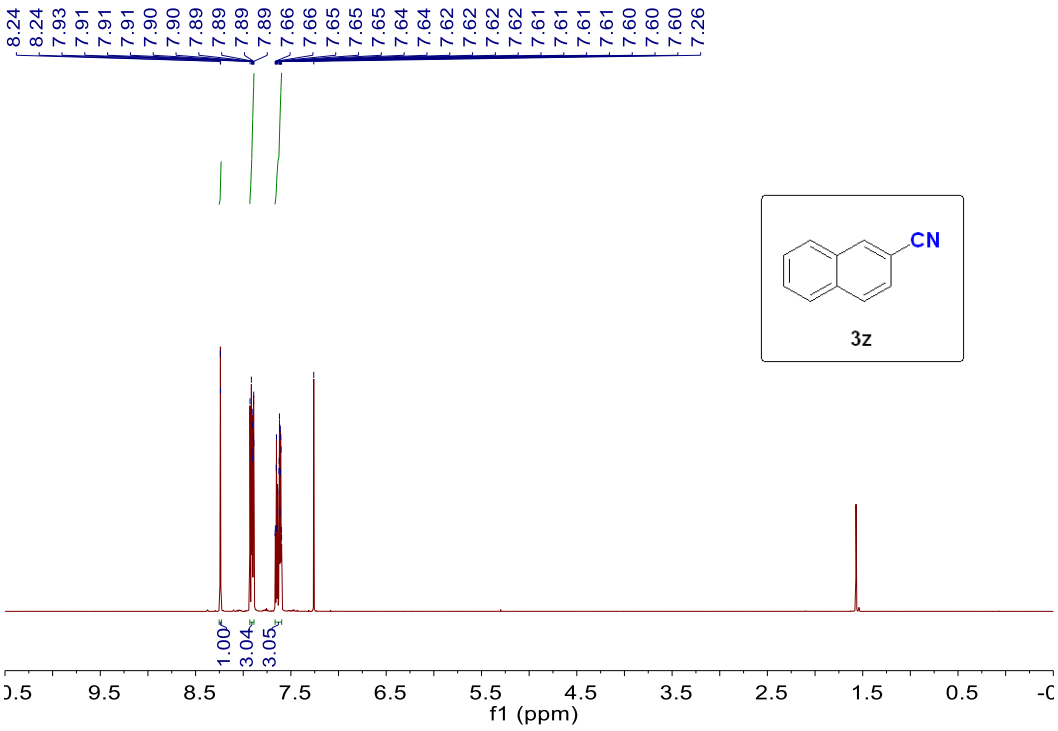
^{1}H NMR (600 MHz) spectrum of **3w** ($CDCl_3$, rt).



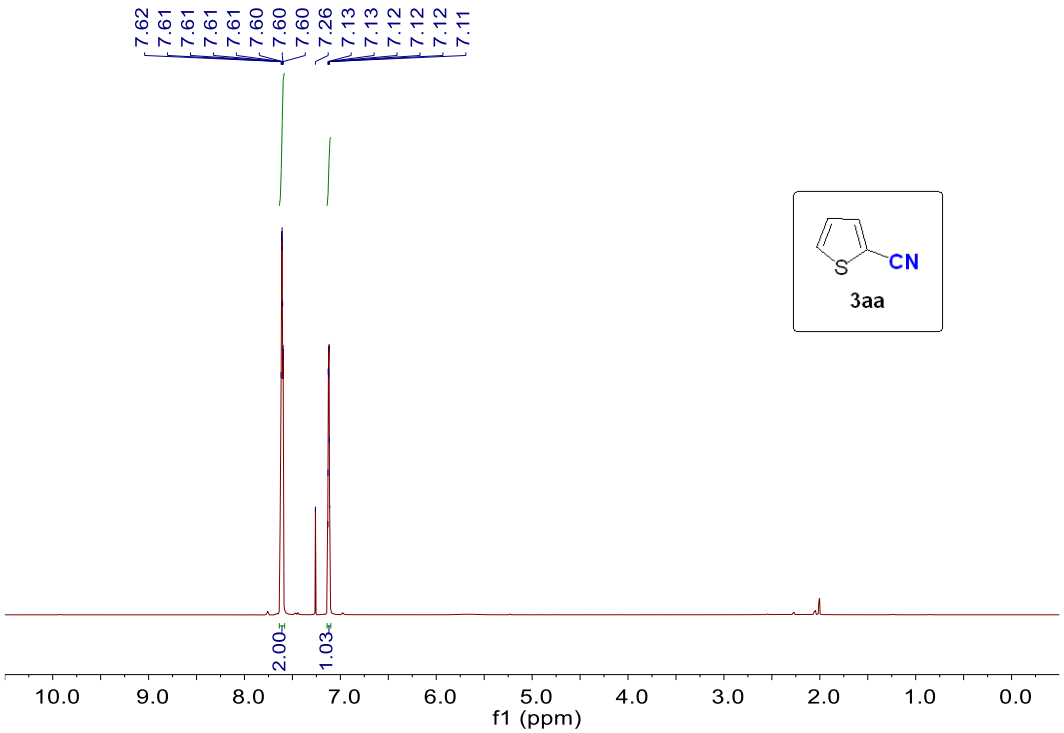
^{1}H NMR (600 MHz) spectrum of **3x** ($CDCl_3$, rt).



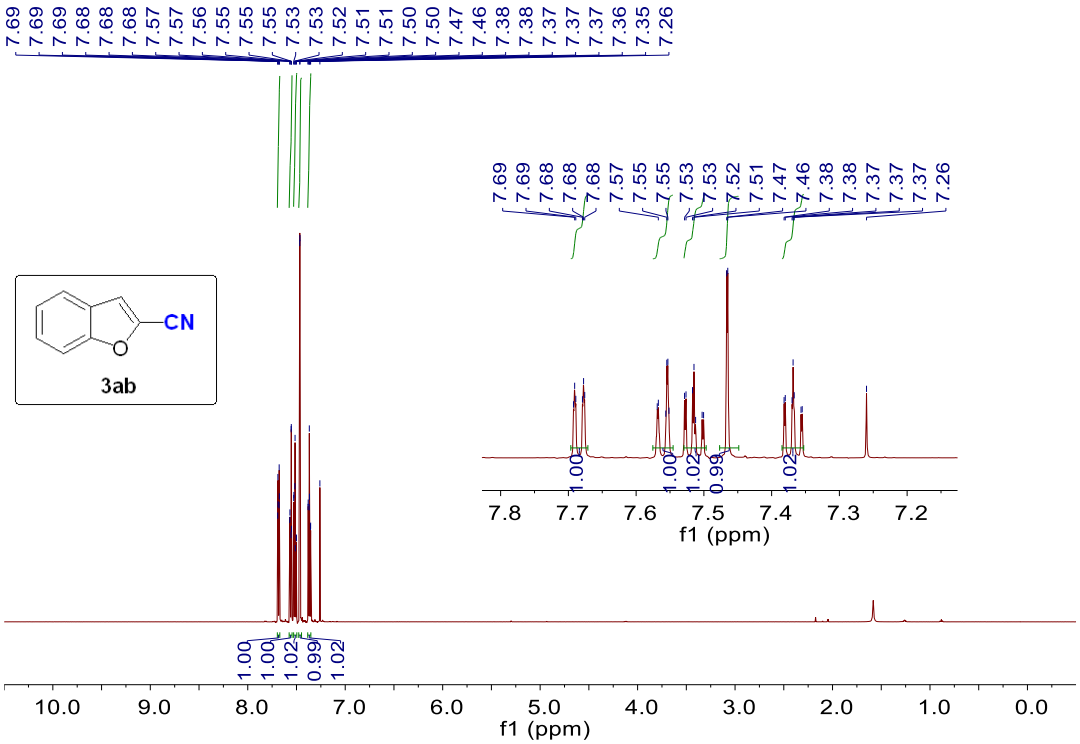
^{1}H NMR (600 MHz) spectrum of **3y** ($CDCl_3$, rt).



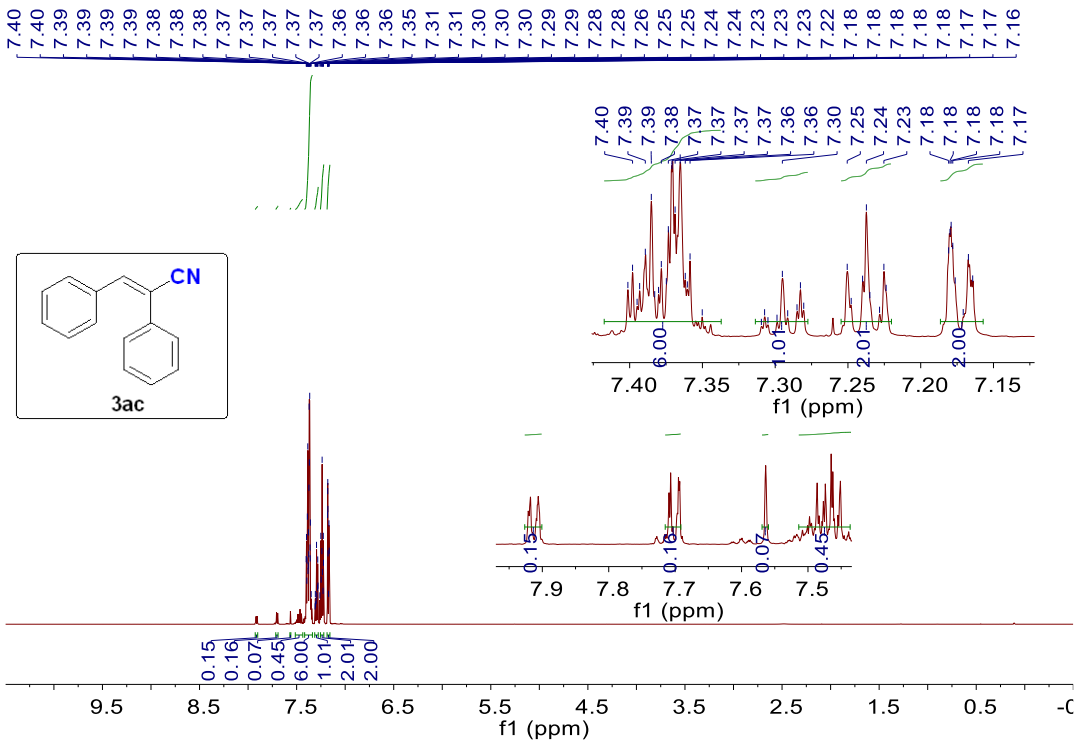
^{1}H NMR (600 MHz) spectrum of **3z** ($CDCl_3$, rt).



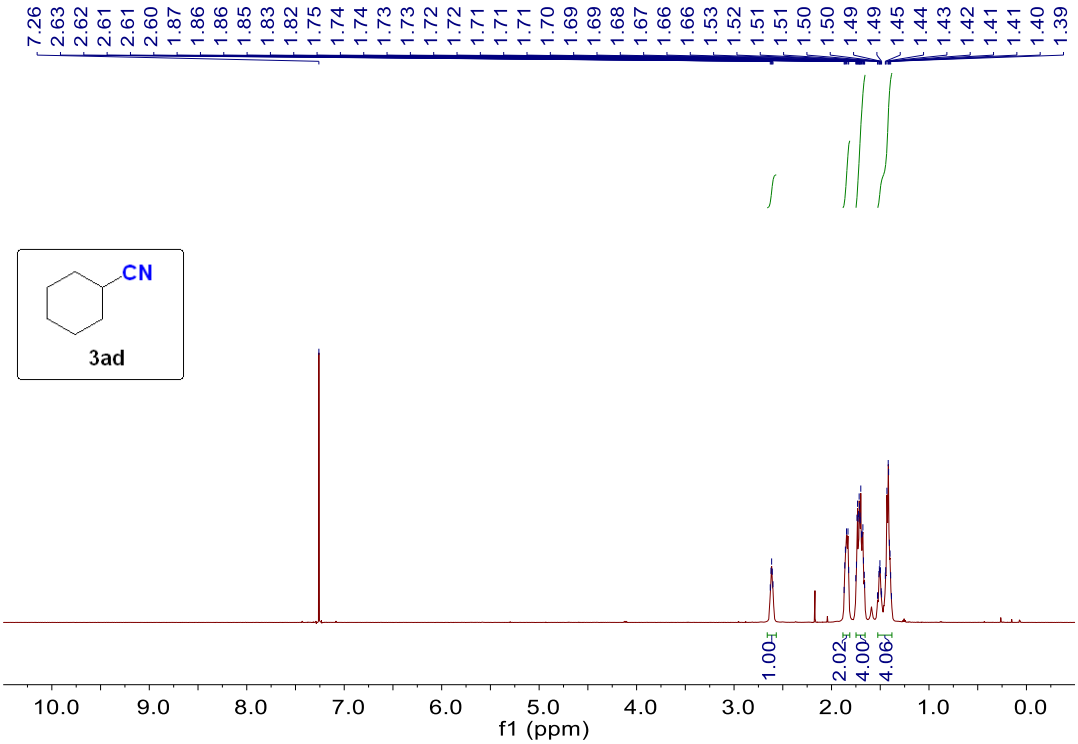
^{1}H NMR (400 MHz) spectrum of **3aa** ($CDCl_3$, rt).



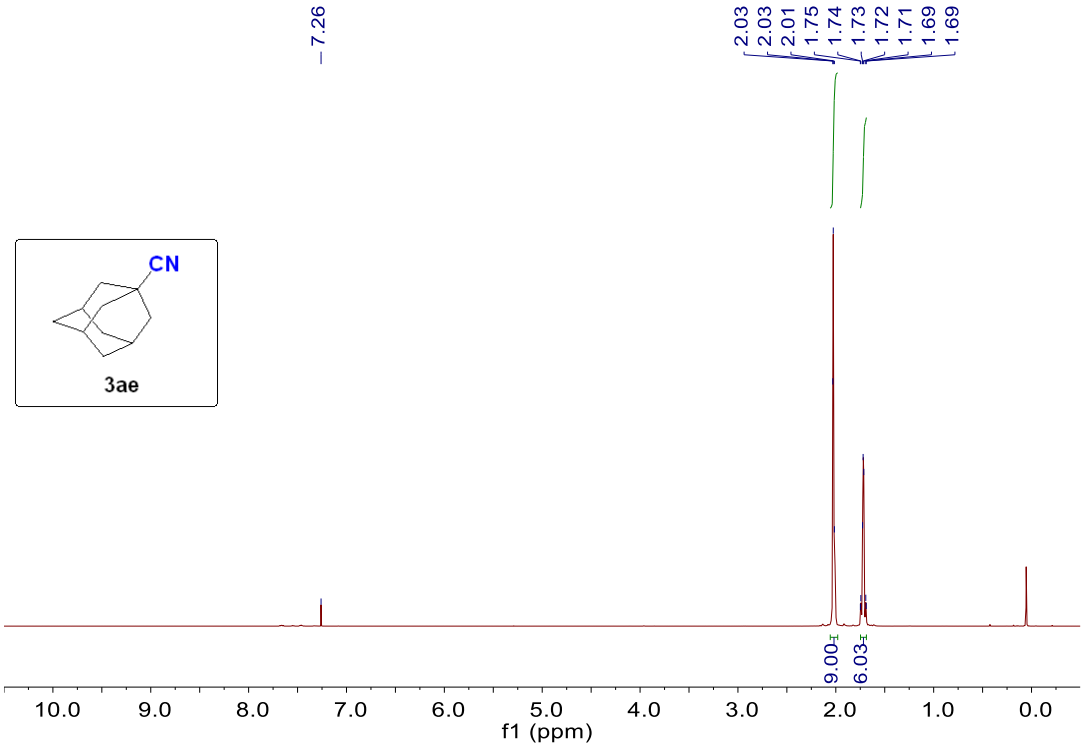
^{1}H NMR (600 MHz) spectrum of **3ab** ($CDCl_3$, rt).



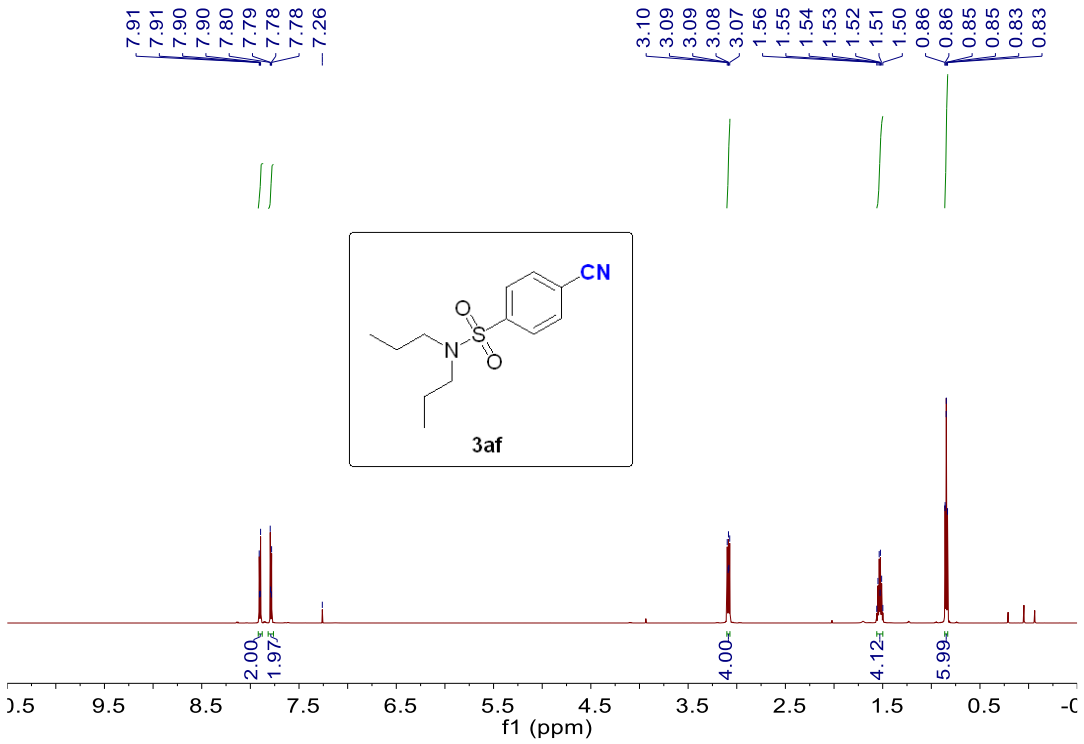
^{1}H NMR (600 MHz) spectrum of **3ac** ($CDCl_3$, rt).



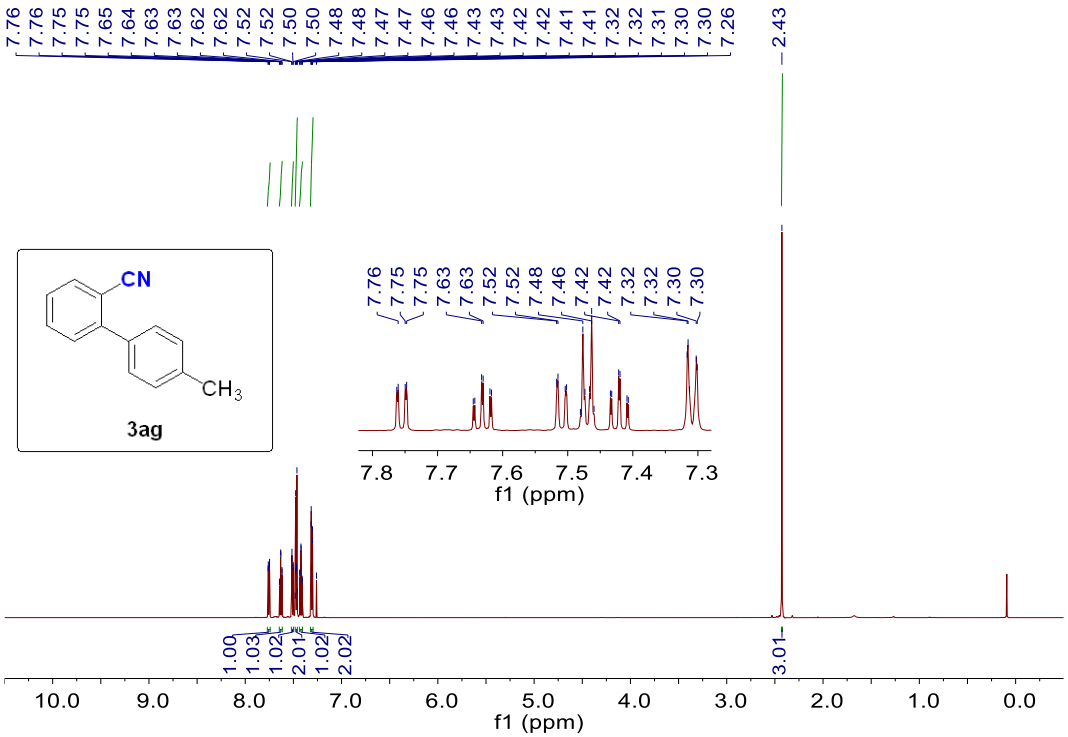
^{1}H NMR (600 MHz) spectrum of **3ad** ($CDCl_3$, rt).



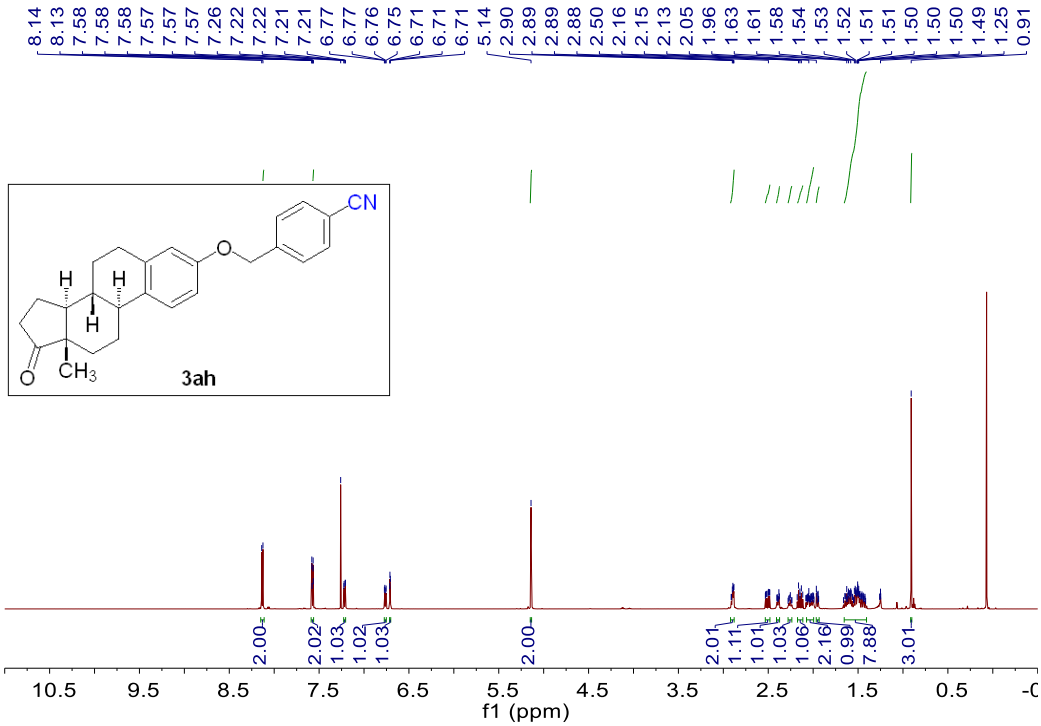
^{1}H NMR (600 MHz) spectrum of **3ae** ($CDCl_3$, rt).

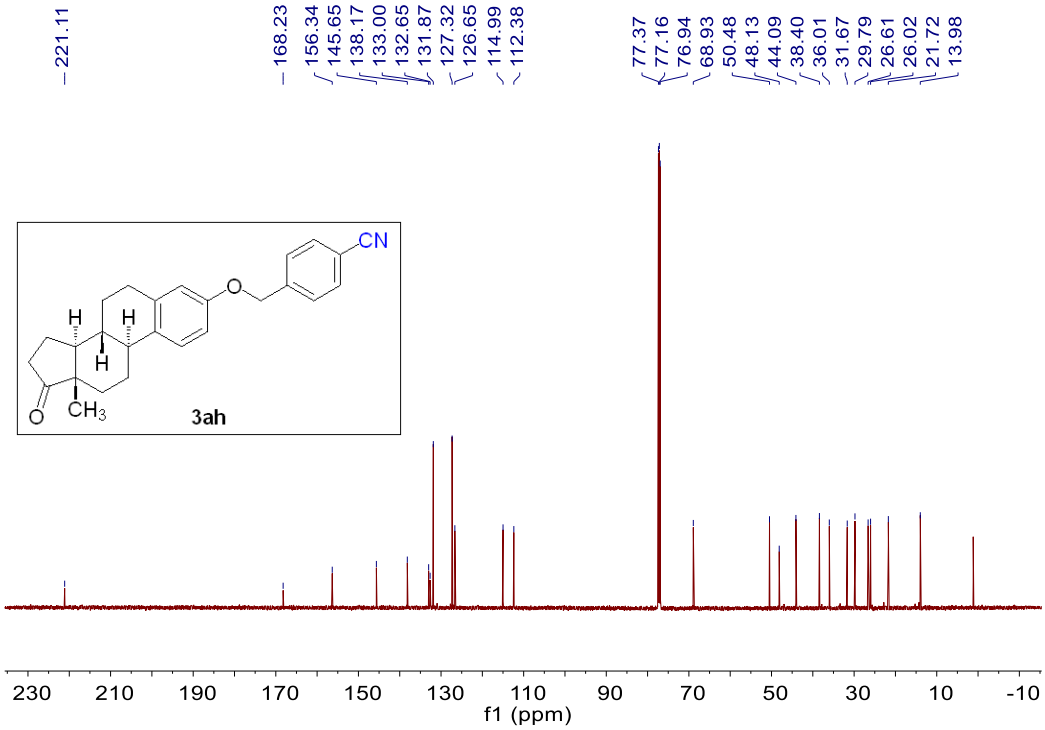


^{1}H NMR (600 MHz) spectrum of **3af** ($CDCl_3$, rt).

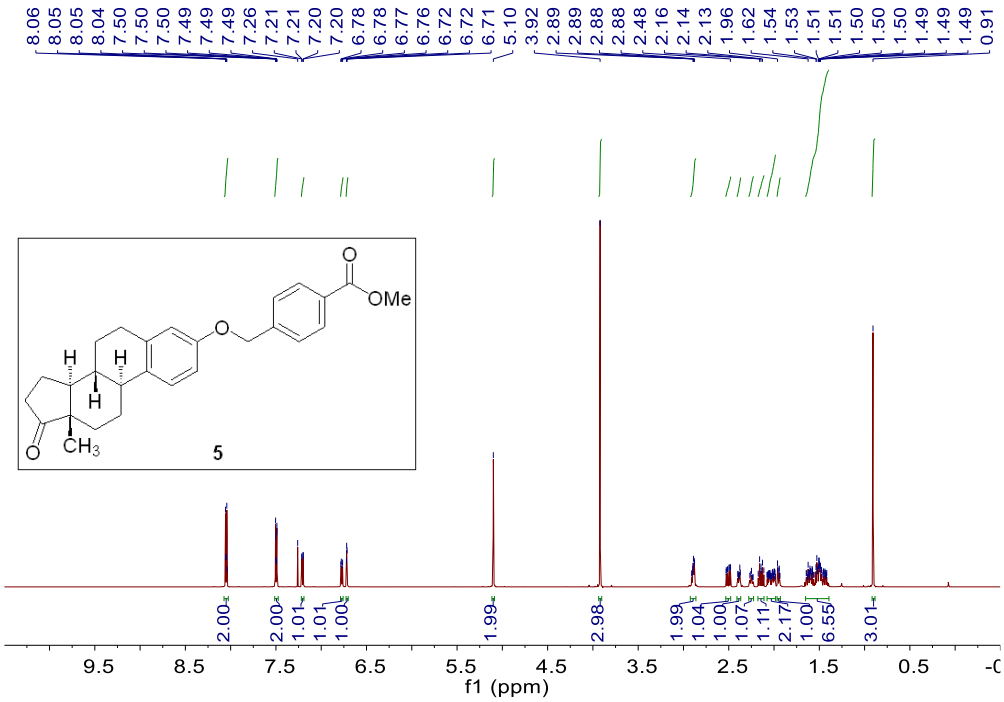


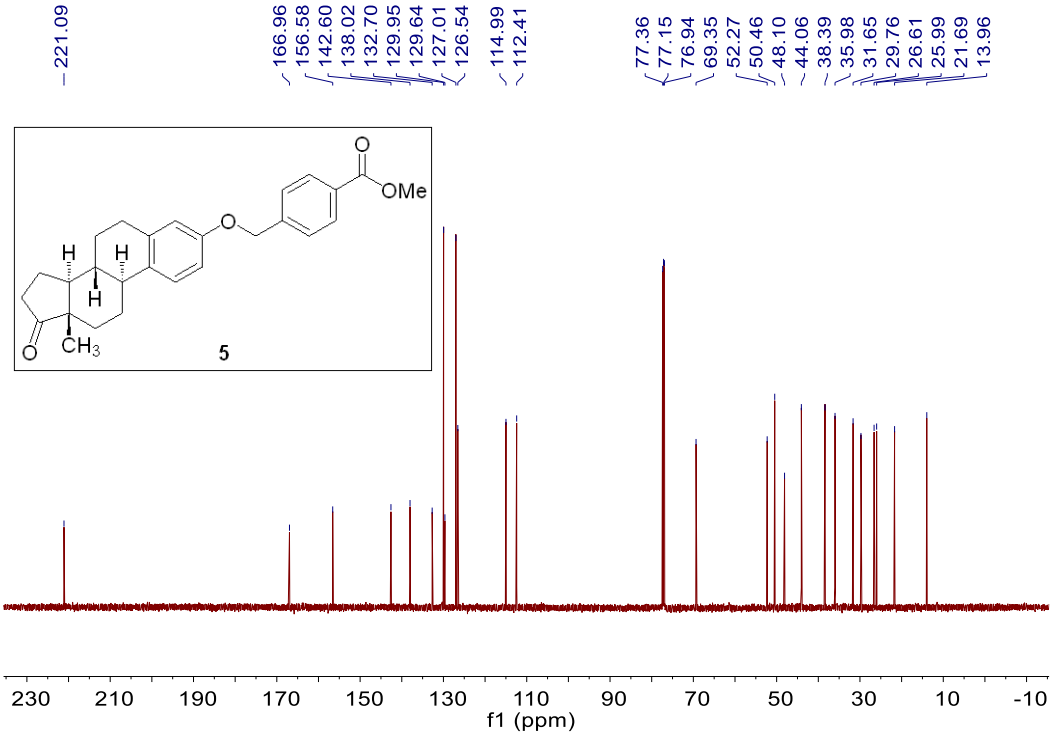
^{1}H NMR (600 MHz) spectrum of **3ag** ($CDCl_3$, rt).



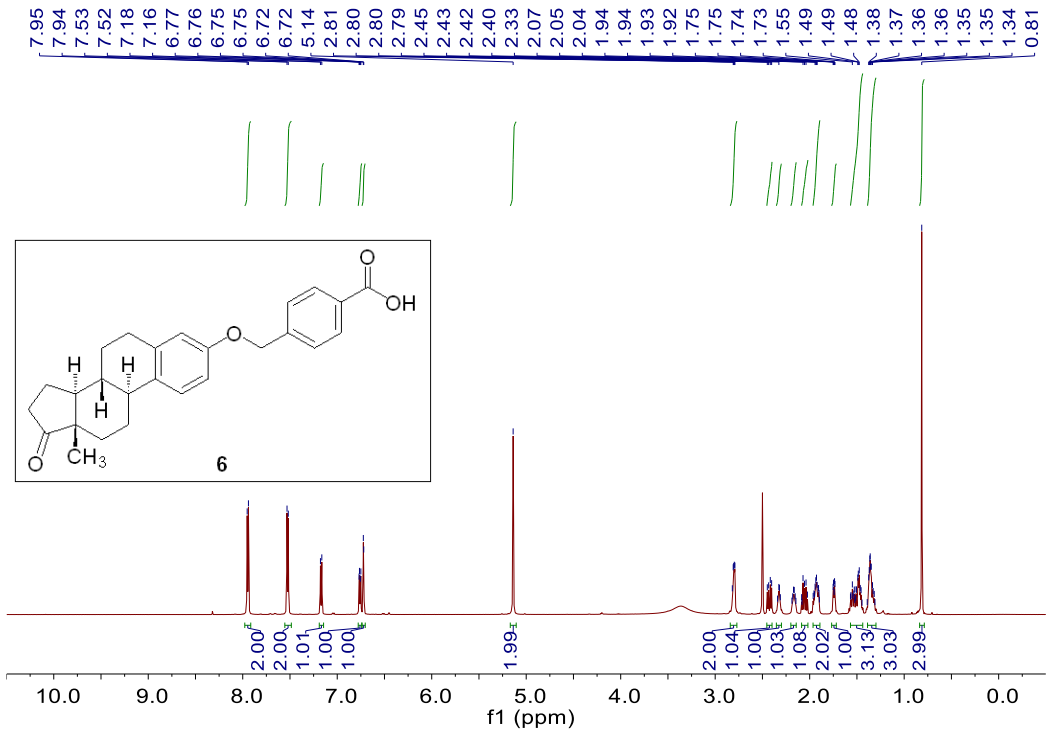


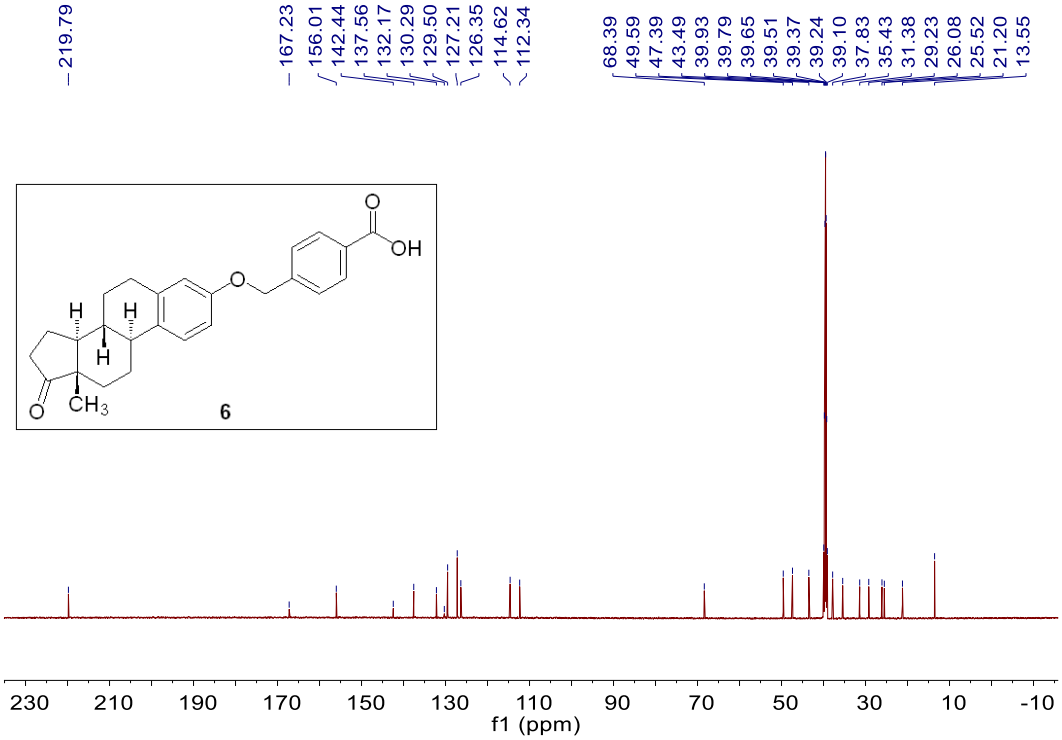
^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra of **3ah** ($CDCl_3$, rt).



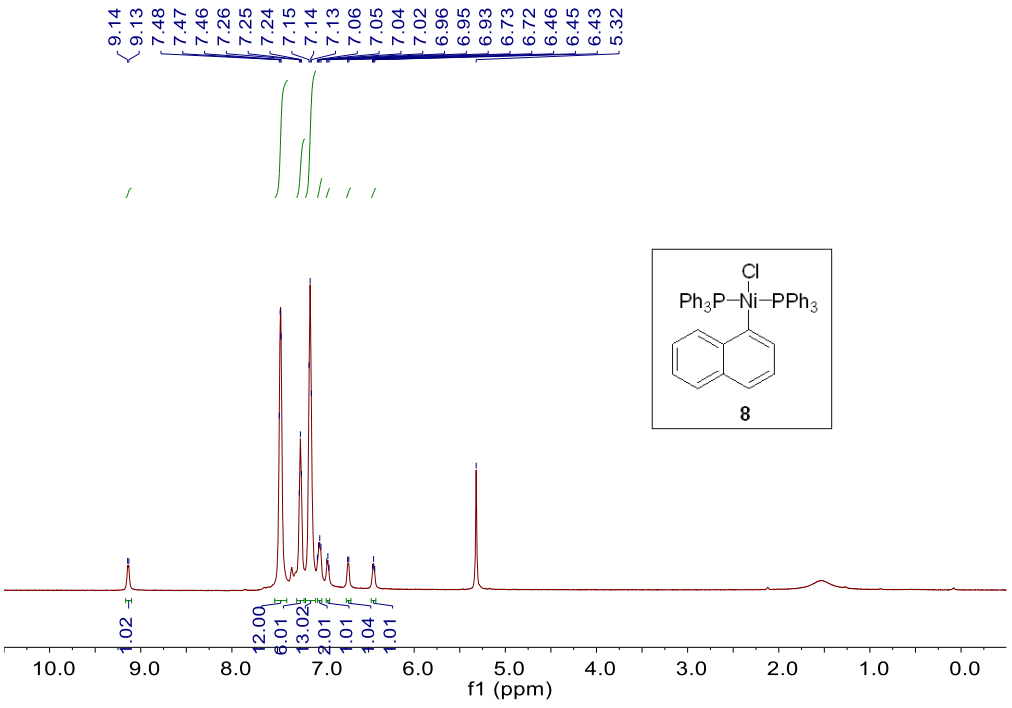


^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra of **5** ($CDCl_3$, rt).

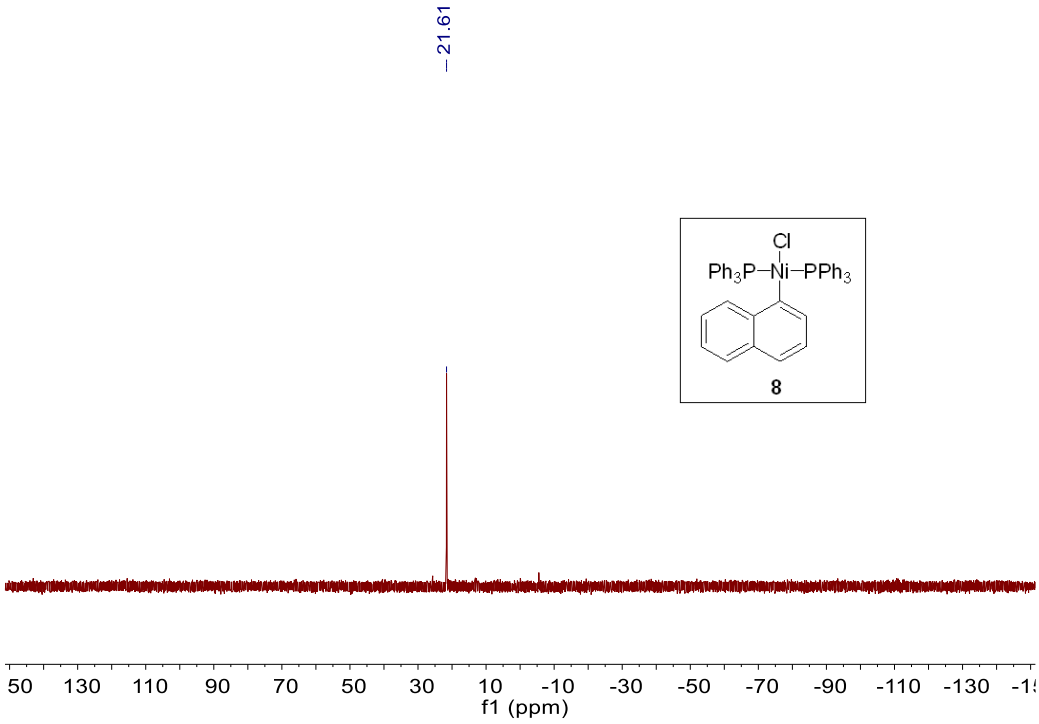




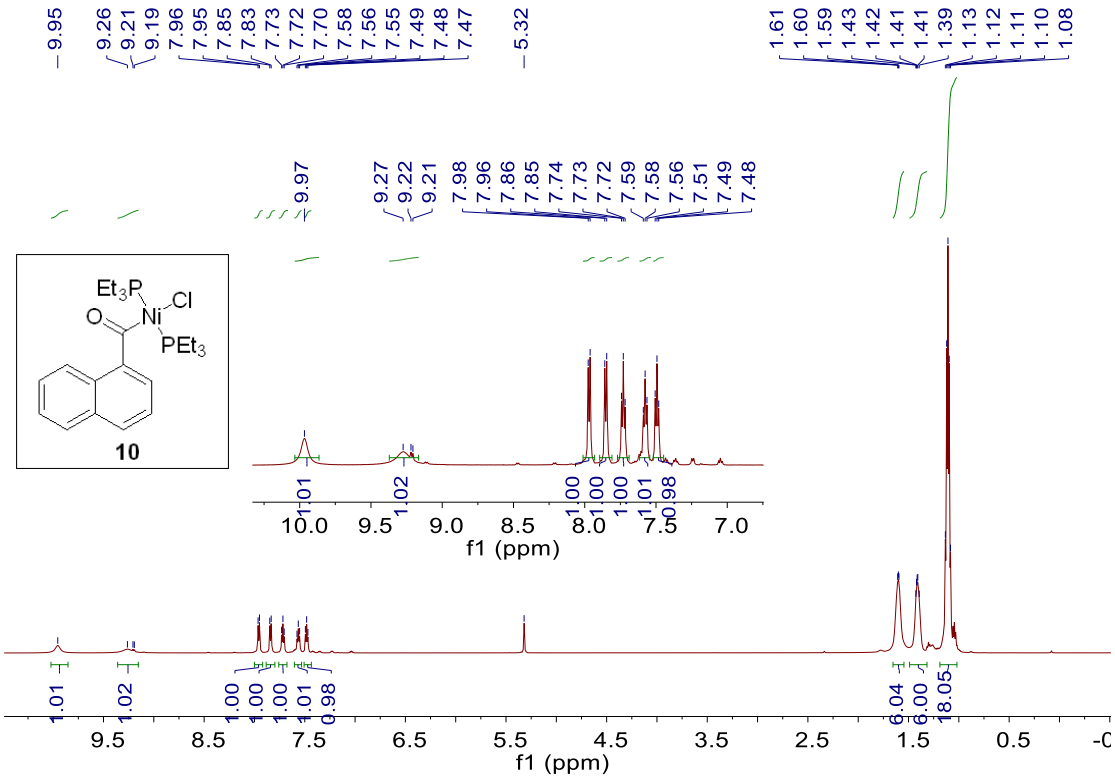
^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra of **6** ($(CD_3)_2SO$, rt).

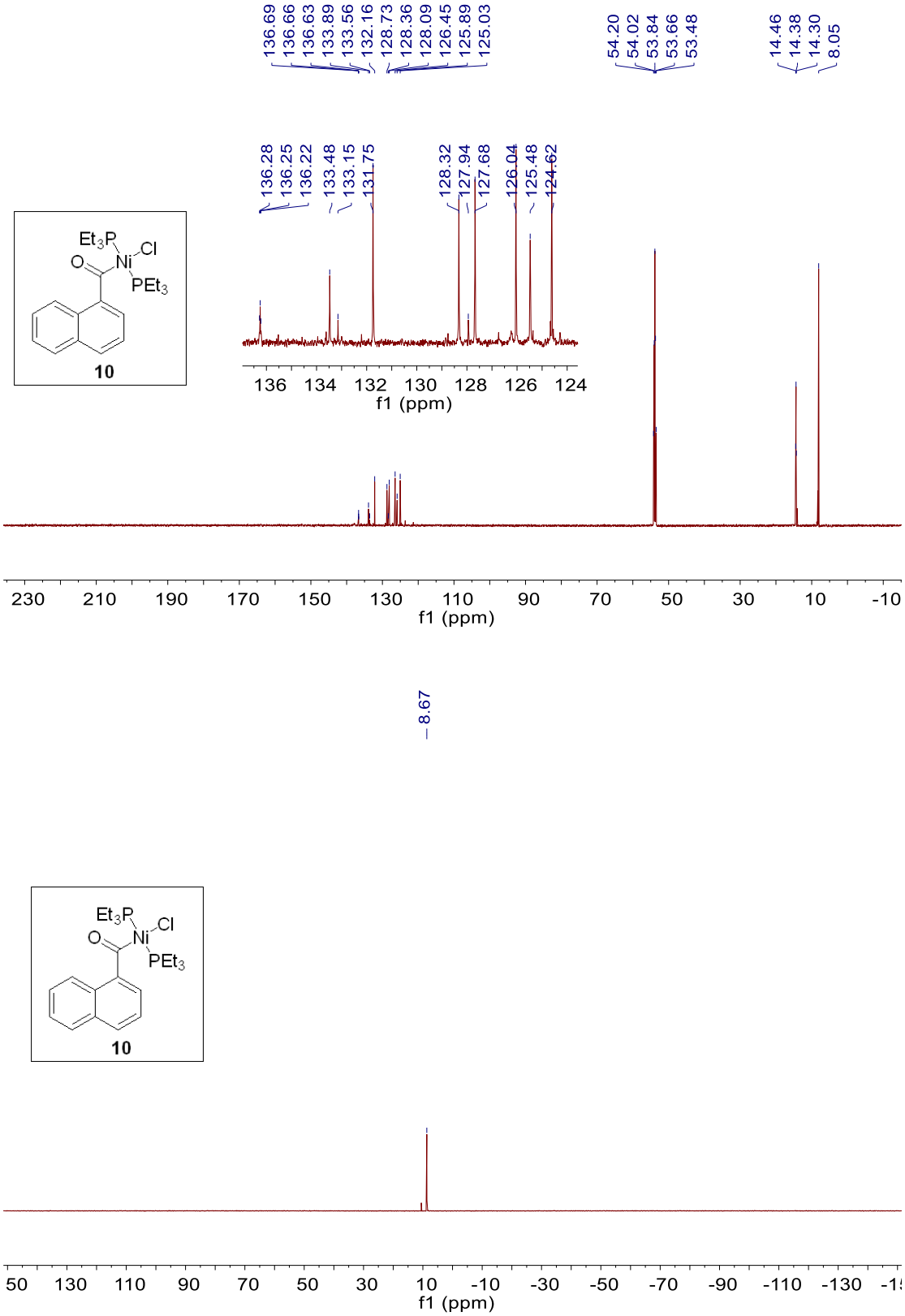


^{1}H NMR (600 MHz) spectrum of **8** (CD_2Cl_2, rt).

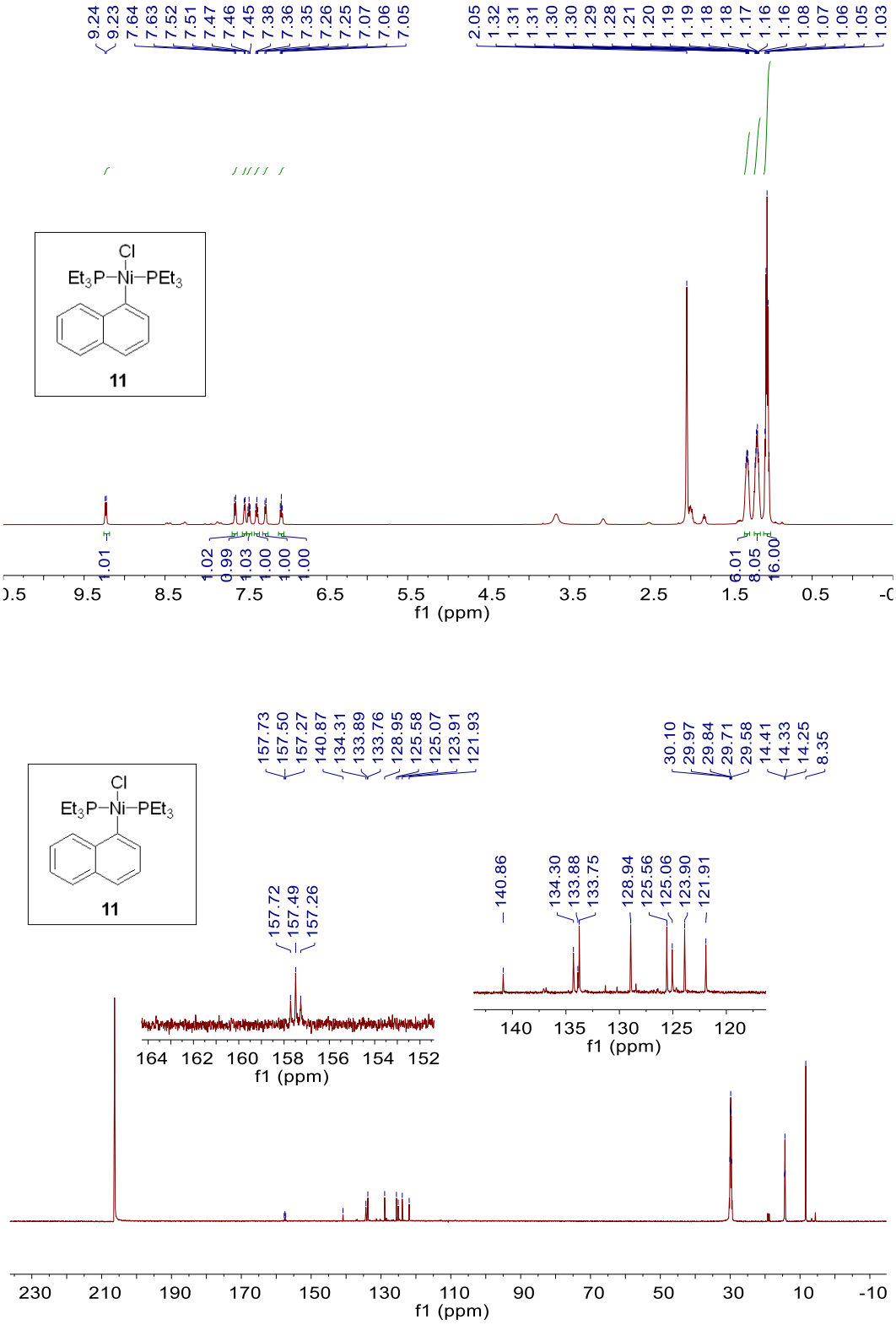


$^{31}P\{^{1}H\}$ NMR (243 MHz) spectrum of complex **8** (C_6D_6, rt).

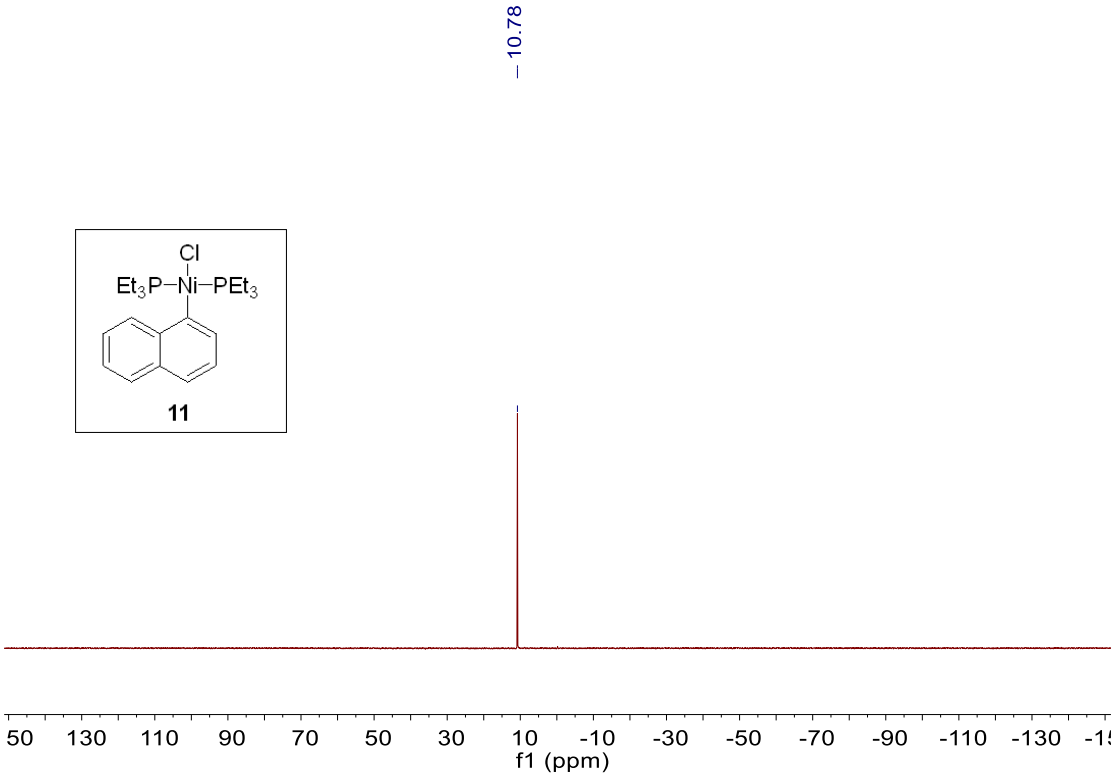




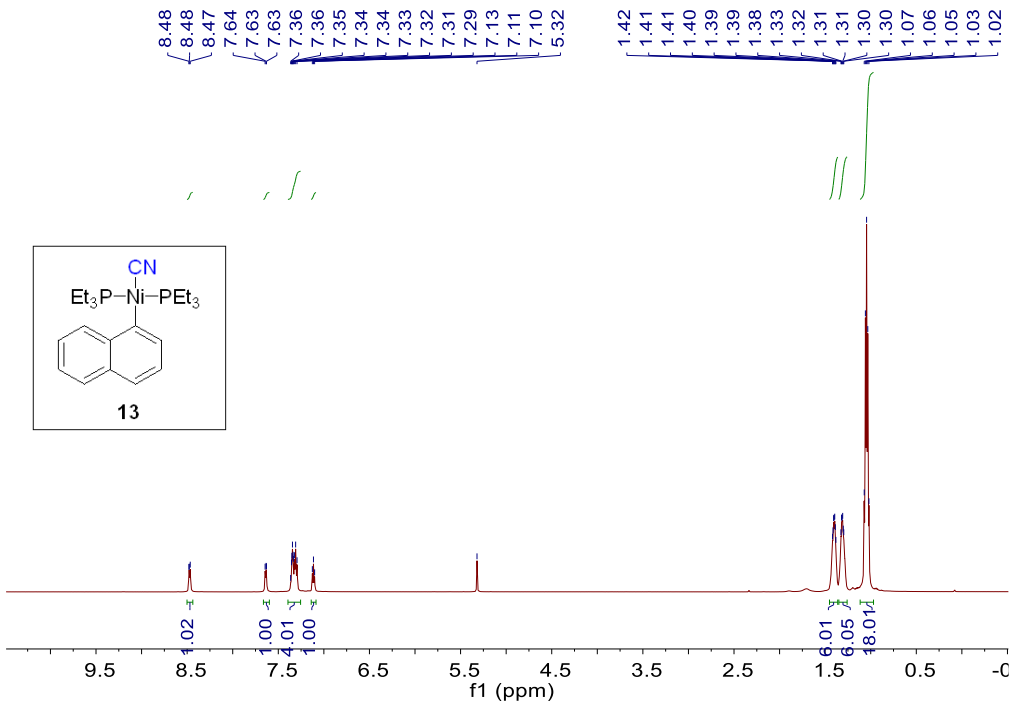
^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz) and ^{31}P NMR (243 MHz) spectra of complex **10** (CD_2Cl_2, rt).

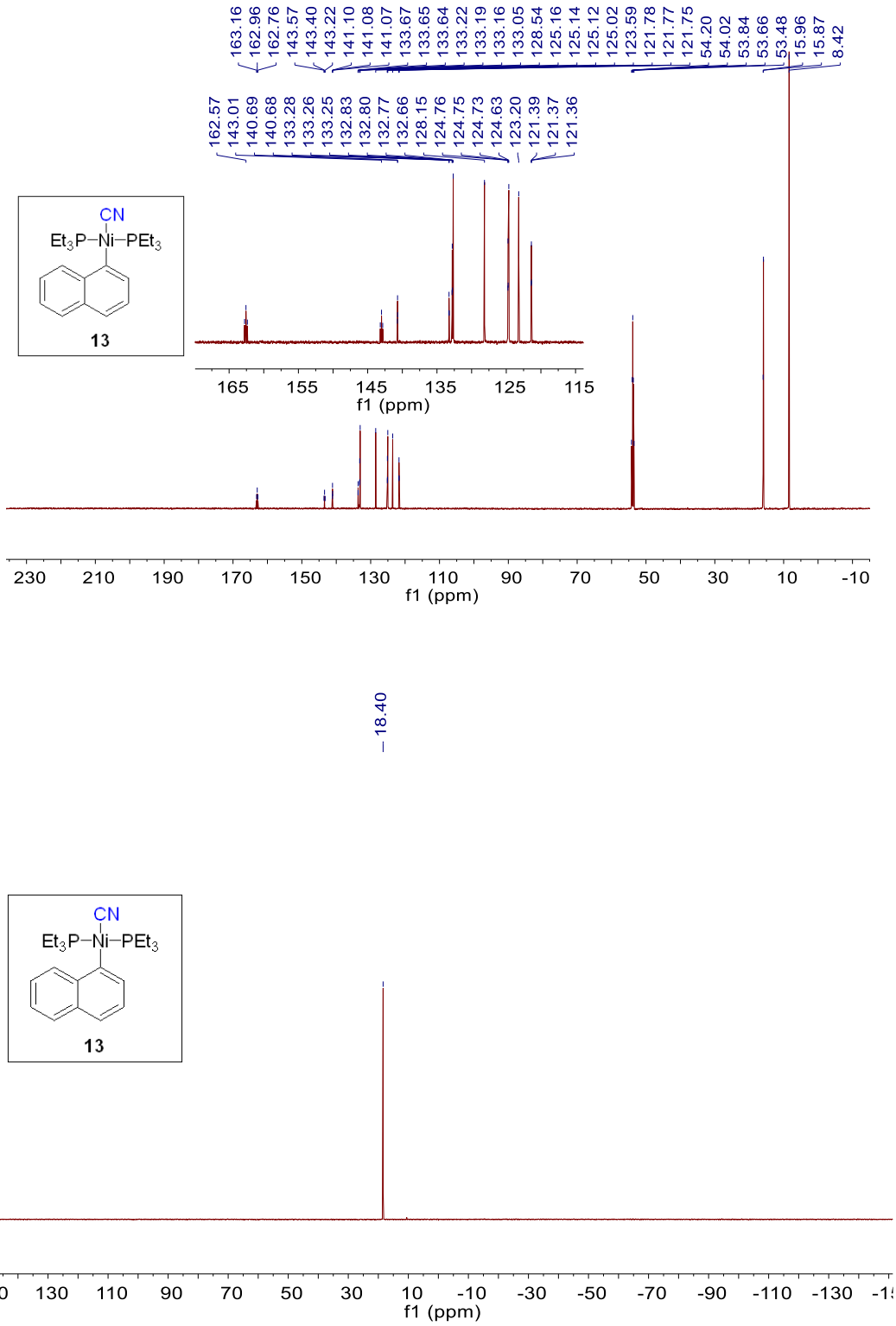


^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra of **11** ($(CD_3)_2CO$, rt).



^{31}P NMR (243 MHz) spectrum of complex **11** (C_6D_6, rt).





^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz), and ^{31}P NMR (243 MHz) spectra of complex **13** (CD_2Cl_2, rt).

2-5. References

1 (a) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical substances: syntheses, patents, applications*, 4th ed.; Georg Thieme: Stuttgart, 2001. (b) Brunton, L.; Chabner, B.; Knollman, B. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*; MacGraw-Hill: New York, 2010. (c) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem*. **2010**, *53*, 7902-7907. (a) Mowry, D. T. *Chem. Rev*. **1948**, *42*, 189-283.

2 (a) Rappoport, Z. *Chemistry of the Cyano Group*; John Wiley & Sons: London, 1970. (b) Rappoport, Z. *The Chemistry of the Cyano Group*; Wiley: New York, 1971. (c) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991. (d) Larock, R. C. *Comprehensive Organic Transformations*; Wiley: New York, 1999.

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CHAPTER 3

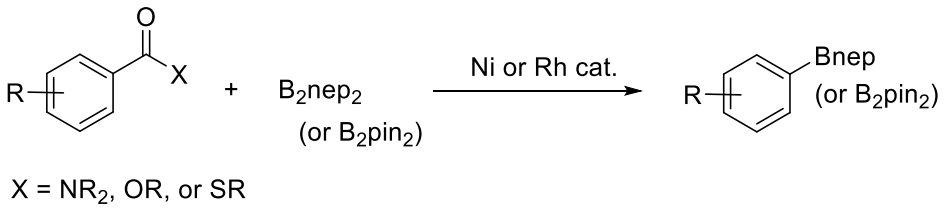
Nickel-Catalyzed Decarbonylative Borylation of Acyl Fluorides

3-1. Introduction

Arylboronic acids and arylboronates are versatile reagents in synthetic organic chemistry.[1] In this Chapter, the synthesis of arylboronates in a decarbonylative manner are systematically elucidated. These compounds are conventionally synthesized by organolithium or -magnesium compounds, which do not tolerated functional groups.[2] The further development of transition-metal-catalyzed borylation reactions has allowed the synthesis of arylboronates from numerous aryl iodides, bromides, chlorides, or triflates.[3] In recent years, much efforts have been devoted to synthesize arylboronates via C−X (X = H,[4] halogen,[5] SR,[6] OR,[7] CN,[8] or NR_2[9]) bond activation.

On the other hand, carboxylic acids are earth abundance and easily available. Facile diversification of carboxylic acids into organoboron compounds shows high value.[10] As such, several examples have succeeded in transformation of carboxylic acid amides,[11,12,] esters, [13,14,15,] thioesters[16,17] and chloride[18] into the corresponding arylboronates in a decarbonylative manner (Scheme 3-1). Very recently, the decarboxylative borylation of aliphatic and aromatic *N*-hydroxyphthalimide esters, derived from the corresponding carboxylic acids, were also disclosed.[19]

Scheme 3-1. Decarbonylative Borylation of Carboxylic Acid Derivatives.



In this Chapter, the Author introduced the utilization of aroyl fluorides as the electrophilic component in a nickel-catalyzed decarbonylative borylation reaction.

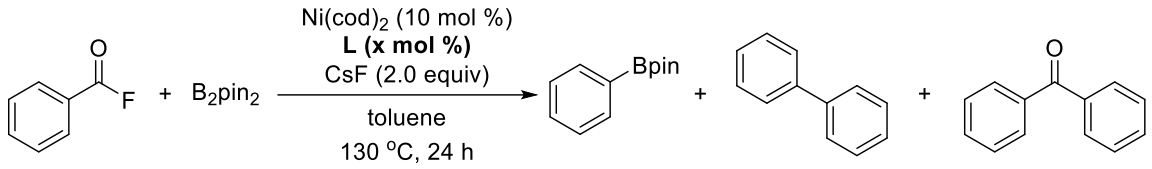
3-2. Results and Discussion

3-2-1 Optimization of the Reaction Conditions

Initial studies involved evaluation of various ligands in the borylation reaction of benzoyl fluoride (**1a**) with bis(pinacolato)diboron (**2a**, $(Bpin)_2$) catalyzed by $Ni(cod)_2$

(Table 3-1). In the presence of CsF, bidentate phosphine ligands frequently used in nickel and catalysis gave no or trace amount decarboylative borylation product **3a** (entries 1-6). Mono dentate phosphine ligands such as PEt_3, P^tBu_3 and $P(C_6F_5)_3$ gave the desired product **3a** less than 5% (entries 7-9). Further ligand screening showed that P^nBu_3 (entry 10), PPh_3 (entry 11) and P(*p*-tol)$_3$ (entry 12) afforded comparable yields. PCy_3 and Ruphos gave inferior results (entries 13 and 14). The strong σ-electron-donating carbene ligand IPr was not suitable in this reaction (entry 15). By slight increasing a loading of the ligand, PPh_3 showed a superior yield than other mono dentate phosphine ligands (entries 16-21). Based on 30 mol % of PPh_3 improving the yield of **3a**, the amount of the ligand was screened (entries 22-25). Higher or lower PPh_3 loading was not good for the conversion of **1a** into **3a** (entries 24 and 25).

Table 3-1. Screening of Ligands.



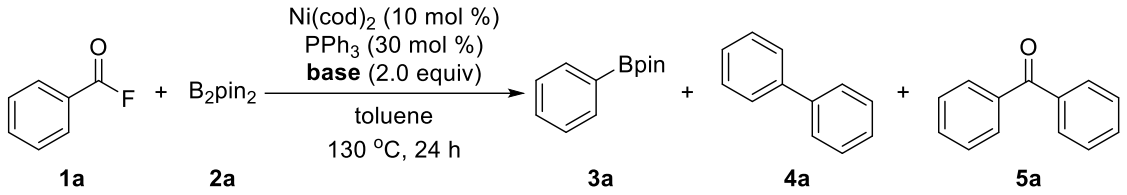
entry[a]	ligand (x mol %)	**1a**[b] (%)	**2a**[b] (%)	**3a**[b] (%)	**4a**[b] (%)	**5a**[b] (%)
1	DPPE (10)	0	157	0	0	1
2	DPPP (10)	0	104	3	0	6
3	DPPF (10)	0	103	3	0	0
4	DCyPE (10)	0	111	1	0	0
5	DPEphos (10)	0	90	5	0	5
6	Xantphos (10)	0	106	1	0	0
7	PEt_3 (20)	0	76	5	0	6
8	P^tBu_3 (20)	0	156	1	0	3
9	$P(C_6F_5)_3$ (20)	4	146	0	0	2
10	P^nBu_3 (20)	0	88	16	0	0
11	PPh_3 (20)	0	137	14	0	<1
12	P(*p*-tol)$_3$ (20)	0	136	12	0	0
13	PCy_3 (20)	0	68	8	0	0

14	Ruphos (20)	0	146	3	0	0
15[c]	IPr·HCl (20)	0	43	2	0	0
16	$^{n}Bu_3P$ (30)	4	56	13	0	0
17	PPh_3 (30)	0	81	23	0	0
18	PPh_2(*o*-tol) (30)	0	122	16	14	2
19	PPh_2Py (30)	0	77	4	0	0
20	PPh_2Cy (30)	0	86	12	0	0
21	$PPh_2(NMe_2C_6H_4)$ (30)	0	76	6	0	0
22	PPh_3 (10)	0	139	3	0	0
23	PPh_3 (20)	0	137	14	0	<1
24	PPh_3 (40)	0	86	6	0	0
25	PPh_3 (50)	0	87	6	0	0

[a]**1a** (0.2 mmol), B_2pin_2 (0.4 mmol), $Ni(cod)_2$ (0.02 mmol) and CsF (0.4 mmol) in toluene (1.0 mL) at 130 °C for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. [c]NaO^tBu (20 mol %) was added.

With PPh_3 as the optimal ligand, various bases were tested. The anion of the base played an important role in this transformation; the bases bearing a fluoride anion gave better results than other anions (Table 3-2, entries 1-12 *vs* 13-16). KF afforded a higher yield than NaF and CsF, suggesting that a counter cation is important to some extent.

Table 3-2. Screening of the Bases.



entry[a]	**base**	**1a**[b] (%)	**2a**[b] (%)	**3a**[b] (%)	**4a**[b] (%)	**5a**[b] (%)
1	LiO^tBu	0	72	4	3	0
2	NaO^tBu	0	116	2	3	0
3	KO^tBu	0	122	<1	5	0
4	Li_2CO_3	0	130	7	4	1
5	Na_2CO_3	0	103	5	4	0

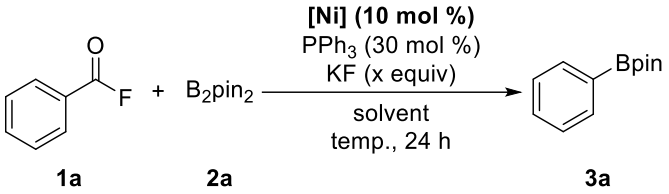
6	K_2CO_3	0	113	6	5	0
7	Cs_2CO_3	0	1	8	4	0
8	K_3PO_4	0	92	4	0	0
9	KOH	0	140	5	1	0
10	KOAc	0	81	4	0	0
11[c]	$LiOCH_3$	10	106	3	0	0
12	PivONa	1	22	3	0	0
13	KPF_6	3	97	10	0	0
14	NaF	30	129	27	1	0
15	KF	0	103	33	4	0
16	CsF	0	81	23	0	0

[a]**1a** (0.2 mmol), B_2pin_2 (0.4 mmol), $Ni(cod)_2$ (0.02 mmol) and PPh_3 (0.06 mmol) in toluene (1.0 mL) at 130 ºC for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

With KF as the best base, several nickel salts were tested. Among $NiCl_2$, $NiBr_2$, $Ni(acac)_2$, $Ni(OAc)_2{\cdot}H_2O$, $NiCl_2$ showed the same reactivity as that of $Ni(cod)_2$, providing **3a** in 32% of GC yield (Table 3-3, entry 2). Since $NiCl_2$ could give an almost same result, it is assumed that a chloride anion is crucial to improve the yield of the present reaction. With this hypothesis in mind, NaCl was added to the reaction mixture. Delightedly, the yield was improved in the presence of NaCl (entries 6 and 7), and **3a** was obtained in 58% with an addition of 2 equiv NaCl (entry 7). Then, the effect of the solvent was investigated, and it is found that toluene was the best choice. In contrast, the high polar solvents are not suitable for this reaction (entries 8-11). 1,4-Dioxane and octane could provide **3a** in 36% and 39% (entries 12 and 14), respectively. By optimizing the amount of the KF, it is found that the yield of **3a** was slightly increasedwhen 2.5 equiv of KF was employed (entry 17). But further increasing of the amount of KF made a decrease of the yield. (entries 18-21). Surprisingly, when a mixture of toluene and octane (v/v = 2: 1) was used, the yield was dramatically increased to 80% (entry 23). The temperature effect of this binary solvent system was also studies, and the yield of **3a** was increased along with elevated the temperature to 140 ºC (entry 24). But no further increase was observed, even though the reaction was conducted at 150 ºC.

Although satisfactory results were obtained at 140 ºC, about 1.0 equiv of diboron still unreacted after reaction. Attempts to decrease the amount of diboron are failed; the yield was decreased as a less amount of **2a** was used (entries 26-28). These results indicates that 2.0 equiv of diboron is important for high product yield in this reaction.

Table 3-3. Screening of the Reaction Conditions.



entry[a]	[Ni]	additive	solvent	KF (eq.)	Temp. (ºC)	**3a**[b] (%)
1	$Ni(cod)_2$	-	toluene	2	130	33
2	$NiCl_2$	-	toluene	2	130	32
3	$NiBr_2$	-	toluene	2	130	14
4	$Ni(acac)_2$	-	toluene	2	130	12
5	$Ni(OAc)_2{\cdot}H_2O$	-	toluene	2	130	4
6	$Ni(cod)_2$	NaCl (1.0)	toluene	2	130	54
7	$Ni(cod)_2$	NaCl (2.0)	toluene	2	130	58
8	$Ni(cod)_2$	NaCl (2.0)	DMSO	2	130	18
9	$Ni(cod)_2$	NaCl (2.0)	DMF	2	130	10
10	$Ni(cod)_2$	NaCl (2.0)	DCE	2	130	<1
11	$Ni(cod)_2$	NaCl (2.0)	NMP	2	130	5
12	$Ni(cod)_2$	NaCl (2.0)	1,4-Dioxane	2	130	36
13	$Ni(cod)_2$	NaCl (2.0)	hexane	2	130	18
14	$Ni(cod)_2$	NaCl (2.0)	octane	2	130	39
15	$Ni(cod)_2$	NaCl (2.0)	toluene	1.0	130	32
16	$Ni(cod)_2$	NaCl (2.0)	toluene	1.5	130	34
17	$Ni(cod)_2$	NaCl (2.0)	toluene	2.5	130	61
18	$Ni(cod)_2$	NaCl (2.0)	toluene	3.0	130	41
19	$Ni(cod)_2$	NaCl (2.0)	toluene	3.5	130	43
20	$Ni(cod)_2$	NaCl (2.0)	toluene	4.0	130	53
21	$Ni(cod)_2$	NaCl (2.0)	toluene	5.0	130	31

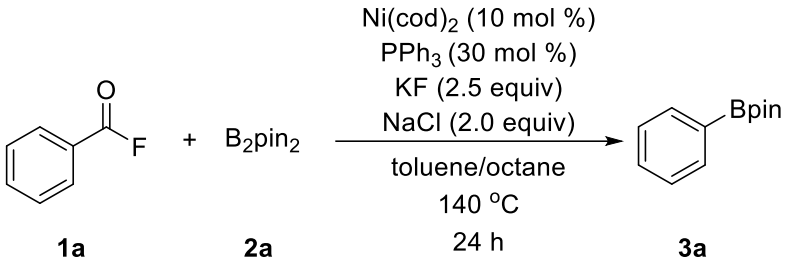
22	$Ni(cod)_2$	NaCl (2.0)	toluene:octane(1:1)	2.5	130	47
23	$Ni(cod)_2$	NaCl (2.0)	toluene:octane(2:1)	2.5	130	80
24	$Ni(cod)_2$	NaCl (2.0)	toluene:octane(2:1)	2.5	140	85 (83)[c]
25	$Ni(cod)_2$	NaCl (2.0)	toluene:octane(2:1)	2.5	150	83
26[d]	$Ni(cod)_2$	NaCl (2.0)	toluene:octane(2:1)	2.5	140	21
27[e]	$Ni(cod)_2$	NaCl (2.0)	toluene:octane(2:1)	2.5	140	52
28[f]	$Ni(cod)_2$	NaCl (2.0)	toluene:octane(2:1)	2.5	140	51

[a] **1a** (0.2 mmol), [Ni] B_2pin_2 (0.4 mmol), PPh_3 (0.06), KF for 24 h. [b] Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. [c] Isolated yield. [d] 1 equiv of **2a** was used. [e] 1.2 equiv of **2a** was used. [f] 1.5 equiv of **2a** was used.

Extensive screening of the reaction conditions revealed that a mixture of 10 mol % of $Ni(cod)_2$, 30 mol % of PPh_3, 2.5 equiv of KF, and 2 equiv of NaCl as the additive at 140 ºC for 24 h in a mixed solvent system, toluene and octane (v/v = 2/1), provided the best result, affording **3a** in 83% yield (Table 3-3, entry 24). The reaction parameters were tested under the optimal conditions, including catalysts, ligands and additives (Table 3-4). Other air-stable Ni(II) salts other than $Ni(cod)_2$ resulted in a lower yield of **3a** (entries 2 and 3). Palladium catalysts such as $Pd(OAc)_2$ and $Pd(dba)_2$ were inefficient (entries 4 and 5). Although $[Rh(OH)(cod)]_2$ was reported to be efficient in decarbonylative borylation of aromatic thioesters,[16] it showed moderate reactivity (entry 6). Replacement of PPh_3 with other monodentate phosphine ligands under identical reaction conditions decreased the yield (entries 7-9). Interestingly, the yield of **3a** was increased in the order of CsF > NaF > KF (Table 3-2), suggesting that a countercation is important to some extent.[20] A similar tendency was observed in the additives; NaCl and KCl afforded good yields, while LiCl, CsCl and TBAC (tetrabutylammonium chloride) gave poor results (entries 10-13). This revealed that suitable countercations may play a vital role in this transformation. These results are associated with recent publications that demonstrate the important role of countercations in C–O bond activation in the reactions of aryl ethers.[21] When no NaCl was added, the yield was slightly decreased to 67% (entry 14). No desired product was detected in the absence of $Ni(cod)_2$ or PPh_3 in the decarbonylative borylation process (entries 15 and 16). The additive KF was found to be essential to proceed the reaction (entry 17), suggesting that an external activator of B_2pin_2 is required. When certain

conditions were applied to the analogous benzoyl chloride at 140 ºC (entry 18) and even at room temperature, 50 ºC, or 80 ºC, no decarbonylative borylation product was detected. It is indicated that a fluoride moiety plays a crucial role and conversion of benzoyl fluoride in situ into benzoyl chloride in the presence of NaCl during this transformation can be ruled out.

Table 3-4. Deviation from Standard Conditions.



entry[a]	deviation from standard conditions	yield of **3a** (%)[b]
1	none	85 (83)[c]
2	$NiCl_2$ instead of $Ni(cod)_2$	52
3	$Ni(OAc)_2{\cdot}4H_2O$ instead of $Ni(cod)_2$	4
4	$Pd(OAc)_2$ instead of $Ni(cod)_2$	16
5	$Pd(dba)_2$ instead of $Ni(cod)_2$	23
6	$[Rh(OH)(cod)]_2$ instead of $Ni(cod)_2$	50
7	PCy_3 instead of PPh_3	16
8	$P(OPh)_3$ instead of PPh_3	46
9	P^nBu_3 instead of PPh_3	71
10	LiCl instead of NaCl	5
11	KCl instead of NaCl	79
12	CsCl instead of NaCl	23
13	TBAC instead of NaCl	25
14	without NaCl	67
15	without $Ni(cod)_2$	0
16	without PPh_3	0
17	without KF	<1
18	benzoyl chloride instead of **1a**	0

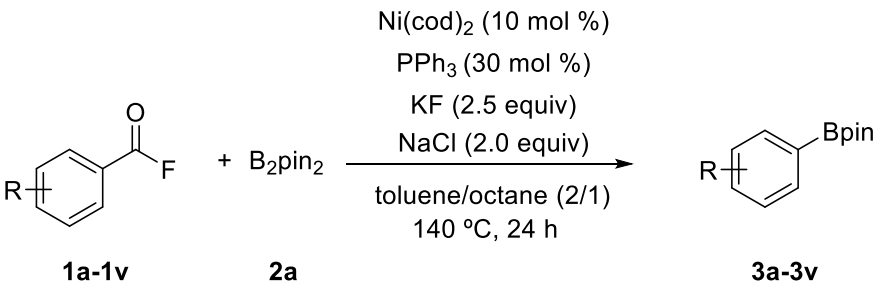
[a] **1a** (0.2 mmol), B_2pin_2 (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol) and NaCl

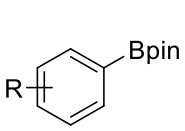
(0.4 mmol) in toluene/octane (v/v = 2/1) at 140 ºC for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. [c]Isolated yield.

3-2-2 Decarbonylative Borylation of Aroyl Fluorides

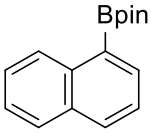
With the optimized conditions in hand, the generality of the reaction was subsequently investigated (Table 3-5). A wide range of electronically and sterically diverse aroyl fluorides with bis(pinacolato)diboron (**2a**) were smoothly converted into the corresponding arylboronates. Aroyl fluorides bearing electron-donating alkyl and alkoxy groups in the *para*-position afforded arylboronates **3b**-**3f** in 50–82% yields. High chemoselectivity of this decarbonylative borylation was demonstrated by the synthesis of **3i** bearing the ester functionality unreacted. This result suggests that this methodology is complementary to the decarbonylative borylation of aromatic esters.[13-15] Moreover, the introduction of electron-withdrawing groups onto benzoyl fluoride led to a slight decrease in the yields of products **3k** and **3l**. Reaction of benzoyl fluoride with ortho-substituents under the identical reaction conditions proceeds smoothly to yield **3n**-**3p**. Naphthyl (**3q** and **3r**), anthracenyl (**3s**), and biphenyl (**3g**, **3m**, and **3t**)-containing arylboronates were successfully obtained in good to high yields. On the other hand, although the decarbonylative borylation using vinyl and benzyl precursors have been elucidated, no traces of the desired products **3** were detected.

Table 3-5. Decarbonylative Borylation of Aroyl Fluorides.

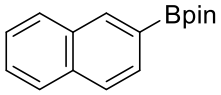




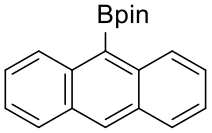
R = H (**3a**): 83%
p-Me (**3b**): 65%
p-^{n}Bu (**3c**): 82%
p-OMe (**3d**): 60%
p-O^{n}Bu (**3e**): 68%
p-OBn (**3f**): 50%
p-Ph (**3g**): 87%
p-NMe_2 (**3h**): 60%
p-CO_2Me (**3i**): 64%
p-COPh (**3j**): 71%
p-CN (**3k**): 45%
p-CF_3 (**3l**): 56%
m-Ph (**3m**): 60%
o-Me (**3n**): 38% (55%)[b]
o-Ph (**3o**): 78%
o-CF_3 (**3p**): 49% (62%)[b]



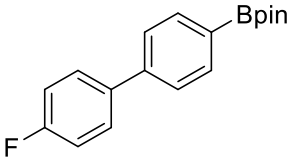
3q: 82%



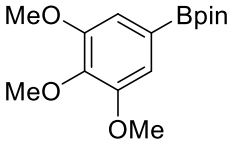
3r: 68%



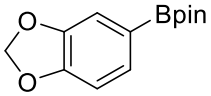
3s: 55%



3t: 71%



3u: 50%

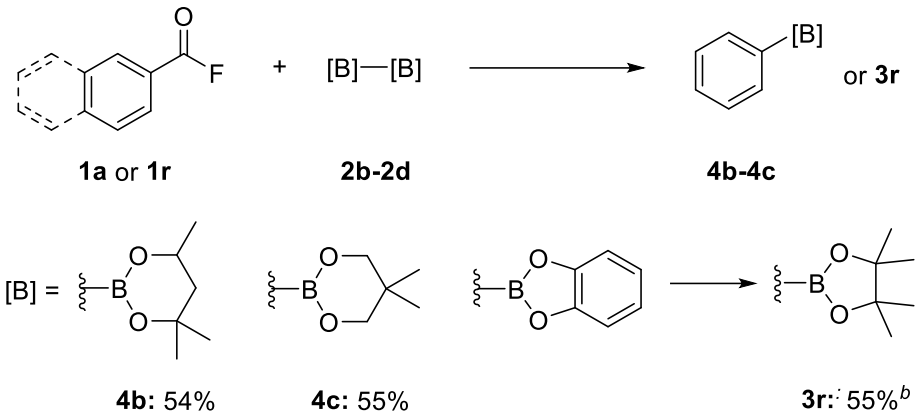


3v: 75%

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h. [b]$Ni(cod)_2$ (0.06 mmol), PPh_3 (0.18 mmol).

To evaluate the utility of this decarbonylative borylation reaction, reactions of a series of diborons have been carried out (Table 3-6). Using bis(hexylene glycolato)diboron (**2b**) and bis(neopentyl glycolato)diboron (**2c**, B_2nep_2) instead of **2a** with benzoyl fluoride (**1a**) gave the corresponding arylboronates **4b** and **4c** in 54% and 55% yields, respectively. The reaction of 2-naphthoyl fluoride (**1r**) with bis(catecholato)diboron (**2d**, B_2cat_2), followed by the replacement with pinacol also yielded in 55% yield.

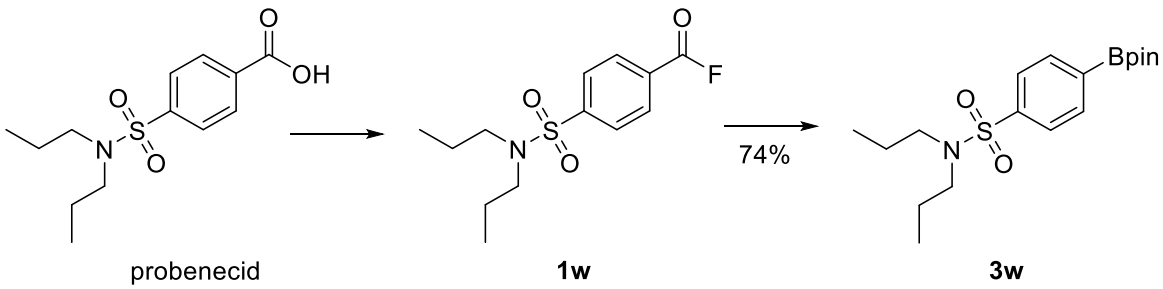
Table 3-6. Elucidation of Other Diborons.[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h. [b]**1r** (0.2 mmol), **2d** (0.4 mmol), then pinacol (4 equiv) and NEt_3 (0.5 mL) at room temperature for 1 h.

This nickel-catalyzed decarbonylative borylation was also viable with complex molecular precursors bearing functional groups. For example, a carboxylic acid-containing drug, probenecid,[22] primarily used to treat gout and hyperuricemia, could be subjected to the two-step fluorination/decarbonylative borylation sequences. After fluorination of probenecid by conventional methods,[23] acyl fluoride **1w** was smoothly converted into the target arylboronate **3w** in 74% yield (Scheme 3-2), whereas the attempt to elucidate the one-pot synthesis of arylboronates without isolation of acyl fluorides was found to be unsuccessful. Delightedly, this decarbonylative borylation is applicable to a large-scale synthesis. The 10-mmol scale experiment provided 1.19 g of **3a** in 58% yield.

Scheme 3-2. Two-Step Borylation of Probenecid.[a]



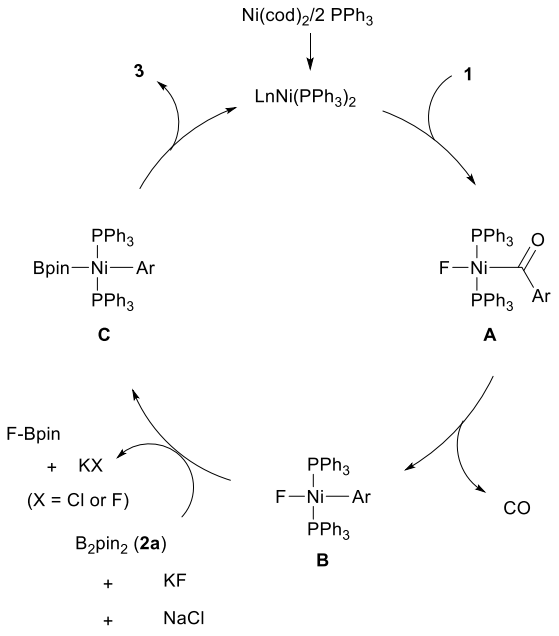
[a]Reaction conditions: **1w** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5

mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h.

3-2-3 Mechanistic Studies

The proposed mechanism of decarbonylative borylation of acyl fluorides is shown in Scheme 3-3. Initially, oxidative addition of acyl fluorides to Ni(0) generates the acyl-nickel(II) intermediate **A**.[24,25,26] Although on attempt to isolate **A** was unsuccessful, some clues for arylnickel species **B** were found. The reaction of $Ni(cod)_2$/ 2 PPh_3 with benzoyl fluoride in C_6D_6 at rt provided a characteristic broad singlet at 409.9 ppm in the $^{19}F\{^1H\}$ NMR spectrum and a doublet at 15.1 ppm with a J_{P-F} of 44 Hz in the $^{31}P\{^1H\}$ NMR spectrum even after 1 h. Considering the results obtained by Sanford,[26] the formed oxidative adduct $Ni(COPh)F(PCy_3)_2$ caused decarbonylation to form $Ni(Ph)F(PCy_3)_2$ at room temperature within 10 min, in this case, the in-situ generated $Ni(COPh)F(PPh_3)_2$ must be more unstable due to the weak coordination ability of PPh_3 than PCy_3. It is concluded that the subsequent extrusion of carbon monoxide forming **B** could take place prior to transmetalation. Transmetalation between complex **B** and B_2pin_2 assisted by external KF (and NaCl) affords borylnickel(II) intermediate **C**. Finally, reductive elimination delivers the targeted arylboronates **3**, regenerating the Ni(0) species to complete a catalytic cycle.

Scheme 3-3. Proposed Mechanism.



3-3. Summary

In summary, we have developed the first decarbonylative borylation of acyl fluorides with the assistance of an abundant and inexpensive metal Ni/PPh_3 catalytic system with B_2pin_2 as a coupling nucleophile has been developed, which is capable of producing various aromatic boronates. Importantly, this method realized that carboxylic acids can be converted into a wide array of arylboronates via acyl fluorides.

3-4. Experimental Section

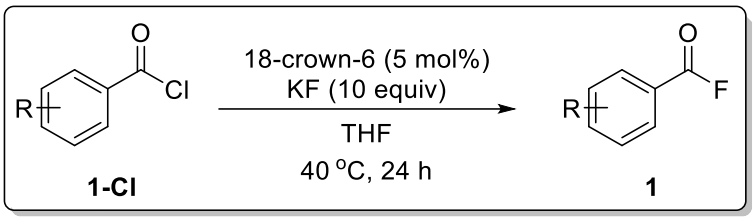
3-4-1 General Instrumentation and Chemicals

Unless otherwise noted, all the reactions were carried out under an Ar atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 ºC) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using silica gel 60 N (spherical, neutral, 40-100 μm) from Kanto Chemicals Co., Ltd. NMR spectra (^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H}) were recorded on Varian INOVA-600 (600 MHz), Mercury-400 (400 MHz), or 300-NMR ASW (300 MHz) spectrometers. Chemical shifts (δ) are in parts per million related to $CDCl_3$ at 7.26 ppm for ^{1}H and at 77.16 ppm for ^{13}C{^{1}H}. The ^{19}F{^{1}H} NMR spectra were measured by using CCl_3F (δ = 0.00 ppm) as an external standard. The NMR yields were determined using dibromomethane as an internal standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. Infrared spectra were recorded on a Shimadzu IR Prestige-21 spectrophotometer. GC analyses were performed on a Shimadzu GC-14A equipped with a flame ionization detector using Shimadzu Capillary Column (CBP1-M25-025) and Shimadzu C-R6A-Chromatopac integrator. HRMS analyses were obtained by using a double focusing magnetic sector mass spectrometer (JEOL JMS-700 MStation). Elemental analyses were carried out with a Perkin-Elmer 2400 CHN elemental analyzer at Okayama University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Benzoyl fluoride (**1a**) (purity > 98%) was purchased from TCI. Bis(pinacolato)diboron (**2a**) (purity > 99%) was obtained from Sigma-Aldrich Co. Bis(1,5-cyclooctadiene)nickel was purchased from Merck. Triphenylphosphine, *n*-octane, and potassium fluoride (purity > 95%) were obtained from Nacalai Tesque. *n*-Dodecane and sodium chloride (purity > 99%) were purchased from Kanto Chemical Co. Acyl fluorides **1b**-**1w** were prepared according to the literatures and showed the identical spectra reported.

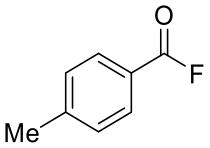
3-4-2 Experimental Procedures

3-4-2-1 Representative Procedure for the Synthesis of Aroyl Fluorides from Acid Chlorides[27]



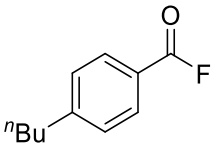
To a 50 mL of Schlenk tube charged with a magnetic stirrer bar, were successively added aroyl chlorides **1-Cl** (4.0 mmol), 18-crown-6 (52.9 mg, 0.2 mmol, 5 mol %), KF (2.32 g, 40 mmol, 10 equiv), and THF (20 mL). After the reaction was stirred at 40 ºC for 24 h, the insoluble inorganic solid (KF or KCl) was filtered, and the volatiles were concentrated using a rotary evaporator. The crude product was purified by bulb-to-bulb distillation to afford the corresponding aroyl fluorides **1** in 44-89% yields.

4-Methylbenzoyl fluoride (1b)[28]



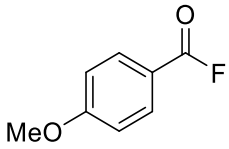
Colorless oil, yield: 46% (254.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.28-7.21 (m, 2H), 7.83-7.89 (m, 2H); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ 17.42.

4-Butylbenzoyl fluoride (1c)[29]



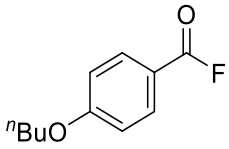
Colorless oil, yield: 84% (605.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.36 (h, J = 7.4 Hz, 2H), 1.60-1.65 (m, 2H), 2.69-2.72 (m, 2H), 7.31-7.34 (m, 2H), 7.92-7.97 (m, 2H); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ 17.41.

4-Methoxybenzoyl fluoride (1d)[30,31]



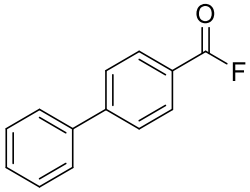
Colorless oil, yield: 50% (308.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 6.98 (dd, J = 9.0, 1.4 Hz, 2H), 7.96-8.02 (m, 2H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ 15.94.

4-Butoxybenzoyl fluoride (1e)[29]



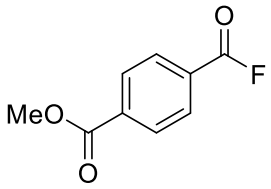
Colorless oil, yield: 87% (682.8 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3H), 1.54-1.47 (m, 2H), 1.82-1.77 (m, 2H), 4.04 (t, J = 6.5 Hz, 2H), 6.99-6.93 (m, 2H), 7.99-7.94 (m, 2H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ 15.75.

[1,1'-Biphenyl]-4-carbonyl fluoride (1g)[32]



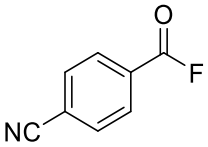
White solid, yield: 68% (544.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.52 (m, 3H), 7.62-7.66 (m, 2H), 7.73-7.76 (m, 2H), 8.10-8.14 (m, 2H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ 18.11.

Methyl 4-(fluorocarbonyl)benzoate (1i)[33]



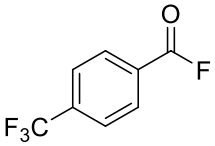
White solid, yield: 60% (437.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 8.10-8.14 (m, 2H), 8.16-8.21 (m, 2H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ 20.06.

4-Cyanobenzoyl fluoride (1k)[28]



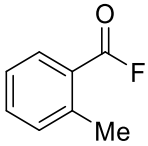
White solid, yield: 80% (477.2 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78-7.82 (m, 2H), 8.21-8.24 (m, 2H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 20.20.

4-(Trifluoromethyl)benzoyl fluoride (1l)[34]



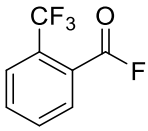
Colorless oil, yield: 58% (445.7 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.85 (m, 2H), 8.19 (d, J = 8.2 Hz, 2H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 19.95, -63.53.

2-Methylbenzoyl fluoride (1n)[28]



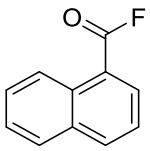
Colorless oil, yield: 44% (243.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (d, J = 1.9 Hz, 3H), 7.29-7.37 (m, 2H), 7.55 (td, J = 7.5, 1.5 Hz, 1H), 7.96-8.02 (m, 1H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 29.15.

2-(Trifluoromethyl)benzoyl fluoride (1p)[35]



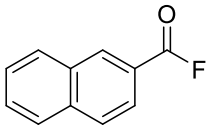
Colorless oil, yield: 50% (384.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.82 (m, 2H), 7.89 (ddt, J = 7.8, 1.4, 0.7 Hz, 1H), 8.04-8.10 (m, 1H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 36.21, -60.50.

1-Naphthoyl fluoride (1q)[31]



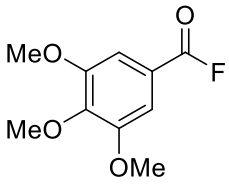
White solid, yield: 89% (620.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.65 (m, 2H), 7.72 (ddd, J = 8.6, 6.9, 1.4 Hz, 1H), 7.95 (ddd, J = 8.2, 1.5, 0.7 Hz, 1H), 8.19 (dt, J = 8.3, 1.2 Hz, 1H), 8.36 (dd, J = 7.4, 1.3 Hz, 1H), 9.02 (dt, J = 8.7, 1.0 Hz, 1H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 18.05.

Methyl 2-naphthoate (1r)[32]



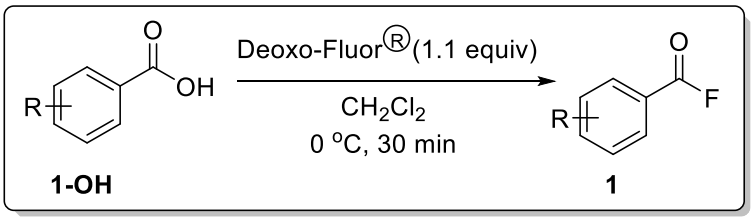
White solid, yield: 60% (418.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.65 (m, 1H), 7.67-7.71 (m, 1H), 7.90-8.03 (m, 4H), 8.65 (s, 1H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 18.04.

3,4,5-Trimethoxybenzoyl fluoride (1u)[28]



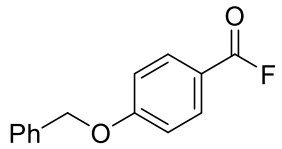
White solid, yield: 72% (616.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 6H), 3.95 (s, 3H), 7.28 (s, 2H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 16.59.

3-4-2-2 Representative Procedure for the Synthesis of Aroyl Fluorides from Carboxylic Acids[36]



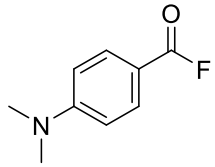
To a 20 mL of Schlenk tube charged with a magnetic stirrer bar, were successively added carboxylic acids **1-OH** (3.0 mmol) and CH_2Cl_2 (15 mL). After the mixture was stirred at 0 ºC, Deoxo-Fluor® reagent (1.1 equiv, 608 µL, 3.3 mmol) was slowly added to the reaction mixture. After the reaction mixture was stirred at 0 ºC for 30 min, the solution was slowly poured into saturated $NaHCO_3$, and after CO_2 evolution ceased it was extracted into CH_2Cl_2 (3 × 15 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography (Hexane:Et_2O = 10:1) to afford the corresponding aroyl fluorides **1** in 22-89% yields.

4-(Benzyloxy)benzoyl fluoride (1f)



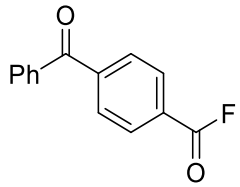
White solid, yield: 28% (193.4 mg), melting point: 105-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (s, 2H), 7.03-7.08 (m, 2H), 7.34-7.46 (m, 5H), 7.97-8.02 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 70.5, 115.4, 117.2 (d, J = 61.2 Hz), 127.6, 128.6, 128.9, 133.9 (d, J = 4.52 Hz), 135.8, 157.4 (d, J = 339.93 Hz), 164.4; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 16.08. FT-IR (neat, cm^{-1}): 640 (s), 688 (m), 740 (m), 842 (s), 1024 (s), 1174 (m), 1213 (s), 1244 (s), 1313 (s), 1384 (s), 1454 (s), 1508 (s), 1579 (s), 1602 (s), 1759 (s), 2945 (s). Anal. Calcd for $C_{14}H_{11}FO_2$: C, 73.03; H, 4.82%. Found: C, 72.99; H, 4.68%.

4-(Dimethylamino)benzoyl fluoride (1h)[37]



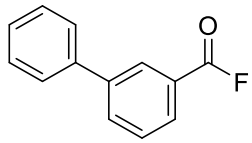
White solid, yield: 22% (110.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (s, 6H), 6.64-6.68 (m, 2H), 7.84-7.89 (m, 2H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 12.32.

4-Benzoylbenzoyl fluoride (1j)



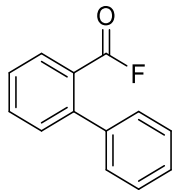
White solid, yield: 47% (321.8 mg), melting point: 125-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.55 (m, 2H), 7.62-7.68 (m, 1H), 7.78-7.83 (m, 2H), 7.90-7.92 (m, 2H), 8.16-8.20 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 128.8, 130.3, 131.5, 131.5 (d, J = 3.47 Hz), 136.5, 143.6, 157.2 (d, J = 338.94 Hz), 195.5; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 19.95. FT-IR (neat, cm^{-1}): 692 (s), 702 (s), 869 (s), 929 (s), 1001 (s), 1026 (s), 1406 (s), 1448 (s), 1651 (s), 1805 (m). HRMS (FAB^{+}): Calcd for $C_{14}H_9FO_2$: 228.0587. Found: 228.0568.

[1,1'-Biphenyl]-3-carbonyl fluoride (1m)[29]



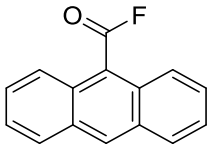
White solid, yield: 68% (408.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.44 (m, 1H), 7.47-7.52 (m, 2H), 7.59-7.64 (m, 3H), 7.9-7.94 (m, 1H), 8.02-8.04 (m, 1H), 8.27 (t, J = 1.8 Hz, 1H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 18.62.

[1,1'-Biphenyl]-2-carbonyl fluoride (1o)[38]



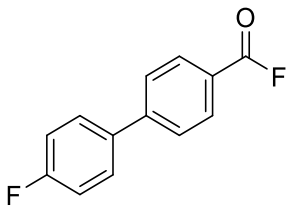
Colorless oil, yield: 50% (300.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.35 (m, 2H), 7.41-7.53 (m, 5H), 7.68 (td, J = 7.6, 1.4 Hz, 1H), 8.04 (dd, J = 7.9, 1.4 Hz, 1H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 34.91.

Anthracene-9-carbonyl fluoride (1s)[29]



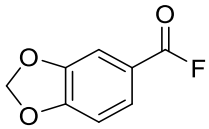
Yellow solid, yield: 57% (383.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55-7.57 (m, 2H), 7.65-7.68 (m, 2H), 8.08 (d, J = 8.4 Hz, 2H), 8.31-8.33 (m, 2H), 8.68 (s, 1H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 59.61.

4'-Fluoro-[1,1'-biphenyl]-4-carbonyl fluoride (1t)[32]



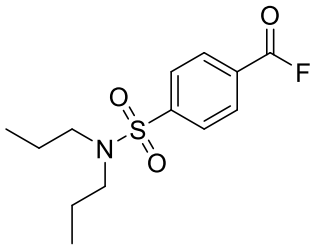
White solid, yield: 48% (314.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.23 (m, 2H), 7.58-7.64 (m, 2H), 7.68-7.72 (m, 2H), 8.09-8.14 (m, 2H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 18.16, −113.02.

Benzo[d][1,3]dioxole-5-carbonyl fluoride (1v)



White solid, yield: 68% (343.0 mg), melting point: 105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 2H), 6.88-6.93 (m, 1H), 7.40-7.43 (m, 1H), 7.67 (ddd, J = 8.2, 1.7, 0.5 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 102.5, 108.7, 110.8 (d, J = 4.1 Hz), 118.5 (d, J = 62.3 Hz), 128.4 (d, J = 4.0 Hz), 148.4, 153.9, 157.0 (d, J = 341.0 Hz); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 16.42. FT-IR (neat, cm^{-1}): 717 (s), 744 (s), 894 (m), 925 (s), 1020 (m), 1265 (m), 1448 (s), 1506 (m), 1797 (s), 2922 (s). Anal. Calcd for $C_8H_5FO_3$: C, 57.15; H, 3.00%. Found: C, 57.14; H, 2.74%.

4-(*N*,*N*-Dipropylsulfamoyl)benzoyl fluoride (1w)

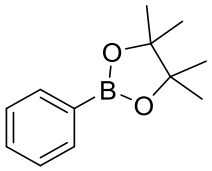


White solid, yield: 31% (267.2 mg), melting point: 76-78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 6H), 1.50-1.60 (m, 4H), 3.09-3.15 (m, 4H), 7.96 (d, J = 8.5 Hz, 2H), 8.18 (d, J = 8.5 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 11.3, 22.1, 50.0, 127.7, 128.1 (d, J = 6.8 Hz), 132.2 (d, J = 3.4 Hz), 146.8, 156.2 (d, J = 345.7 Hz); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ 20.21. FT-IR (neat, cm^{-1}): 682 (s),734 (s), 997 (s), 1024 (m), 1087 (s), 1161 (s), 1240 (m), 1346 (s), 1807 (s), 1824 (s), 2875 (s), 2935 (s), 2974 (s). Anal. Calcd for $C_{13}H_{18}FNO_3S$: C, 54.34; H, 6.31; N, 4.87%. Found: C, 54.58; H, 6.43; N, 4.82%.

3-4-2-3 Ni-Catalyzed Decarbonylative Borylation of Aroyl Fluorides

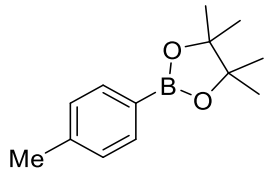
An oven dried Schlenk tube containing a stirring bar was charged with $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 10 mol %), PPh_3 (15.7 mg, 0.06 mmol, 30.0 mol %), toluene (0.66 mL), octane (0.33 mL) and stirring for 30 s at room temperature. Next, aroyl fluoride (0.2 mmol, 24.8 mg), KF (30.6 mg, 0.5 mmol, 2.5 equiv.), bis(pinacolato)diboron (**2a**) (101.6 mg, 0.4 mmol, 2.0 equiv), and NaCl (23.4 mg, 0.4 mmol, 2 equiv) were added. The mixture was heated at 140 ºC with stirring for 24 h. After cooling to room temperature, to the mixture was added saturated aqueous ammonium chloride (ca. 3 mL) and extracted with EtOAc (ca. 3 mL × 3). The combined organic extract was dried over Na_2SO_4, and then filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding final product **3**.

4,4,5,5-Tetramethyl-2-phenyl-1,3,2-dioxaborolane (3a)[39]



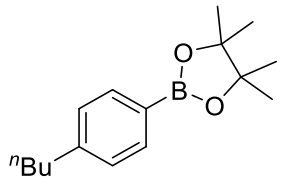
Colorless oil, yield: 83% (33.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 12H), 7.34-7.39 (m, 2H), 7.43-7.49 (m, 1H), 7.81 (dd, J = 8.0, 1.4 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 25.0, 83.9, 127.8, 131.4, 134.9. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.91.

4,4,5,5-Tetramethyl-2-(p-tolyl)-1,3,2-dioxaborolane (3b)[14]



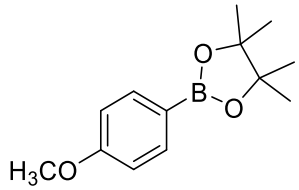
Colorless solid, yield: 65% (28.4 mg), melting point: 53-54 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (s, 12H), 2.37 (s, 3H), 7.17-7.21 (m, 2H), 7.71 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 21.9, 25.0, 83.7, 128.6, 134.9, 141.5. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.93.

2-(4-Butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3c)[39]



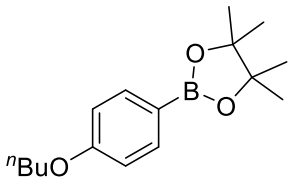
Colorless oil, yield: 82% (42.7 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.34 (s, 14H), 1.58-1.64 (m, 2H), 2.61-2.65 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 14.1, 22.5, 25.0, 33.6, 36.0, 83.7, 128.0, 134.9, 146.5. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.97.

2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3d)[17]



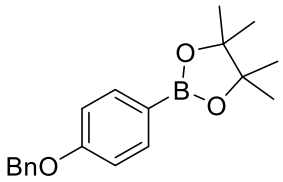
Colorless oil, yield: 60% (28.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (s, 12H), 3.83 (s, 3H), 6.90 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 25.0, 55.2, 83.7, 113.4, 136.6, 162.3. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.83.

2-(4-Butoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3e)[40]



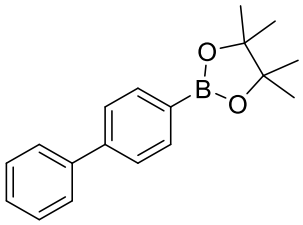
Colorless oil, yield: 68% (37.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.33 (s, 12H), 1.46-1.52 (m, 2H), 1.74-1.79 (m, 2H), 3.99 (t, J = 6.5 Hz, 2H), 6.87-6.91 (m, 2H), 7.71-7.77 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 14.0, 19.4, 25.0, 31.4, 67. 6, 83.6, 114.0, 136.6, 161.9. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.83.

2-(4-(Benzyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3f)[17]



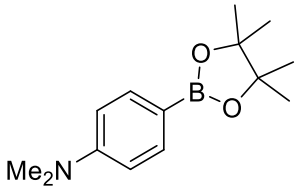
White solid, yield: 50% (31.0 mg), melting point: 85-86 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (s, 12H), 5.10 (s, 2H), 6.96-6.99 (m, 2H), 7.30-7.34 (m, 1H), 7.38 (dd, J = 8.5, 6.7 Hz, 2H), 7.43 (d, J = 7.1 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 25.0, 69.8, 83.7, 114.3, 127.6, 128.1, 128.7, 136.7, 136.9, 161.4. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.80.

2-([1,1'-Biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3g)[17]



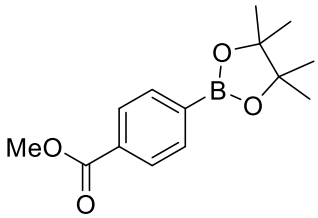
Colorless solid, yield: 87% (48.7 mg), melting point: 118-119 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.37 (s, 12H), 7.34-7.38 (m, 1H), 7.42-7.48 (m, 2H), 7.59-7.65 (m, 4H), 7.89 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 25.0, 84.0, 126.6, 127.4, 127.7, 128.9, 135.4, 141.2, 144.0. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.99.

_N,N_-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3h)[17]



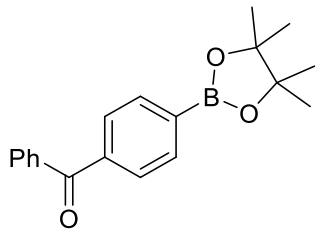
White solid, yield: 60% (29.7 mg), melting point: 114-116 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (s, 12H), 2.99 (s, 6H), 6.70 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 25.0, 40.3, 83.3, 111.4, 136.3, 152.6. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.79.

Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (3i)[17]



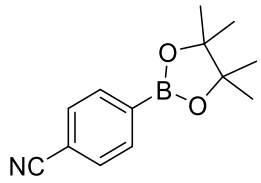
White solid, yield: 64% (33.6 mg), melting point: 79-81 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (s, 12H), 3.90 (s, 3H), 7.86 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 25.0, 52.2, 84.3, 128.7, 132.4, 134.8, 167.2. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.70.

Phenyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (3j)[14]



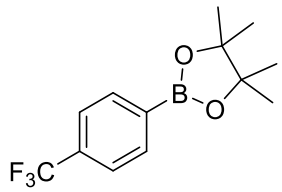
White solid, yield: 71% (43.8 mg), melting point: 110-111 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.37 (s, 12H), 7.48 (dd, J = 8.1, 7.3 Hz, 2H), 7.58 (d, J = 7.5 Hz, 1H), 7.76-7.81 (m, 4H), 7.90-7.93 (m, 2H) ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 25.0, 84.3, 128.4, 129.2, 130.3, 132.7, 134.7, 137.6, 139.9, 197.1. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.66.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (3k)[17]



White solid, yield: 45% (20.6 mg), melting point: 100-101 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (s, 12H), 7.64 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 24.8, 84.4, 114.5, 118.8, 131.1, 135.1. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.42.

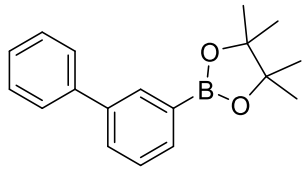
4,4,5,5-Tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (3l)[14]



Colorless solid, yield: 56% (30.5 mg), melting point: 76-77 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.36 (s, 12H), 7.61 (d, J = 7.4 Hz, 2H), 7.92 (d, J = 7.4 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 1.2, 25.0, 84.4, 124.1 (q, J = 272.1 Hz), 124.5 (q, J = 3.7 Hz), 133.0

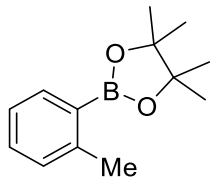
(q, J = 32.2 Hz), 135.2. (The signal for the carbon that is attached to the boron atom was not observed); $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 30.56.

2-([1,1'-Biphenyl]-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3m)[14]



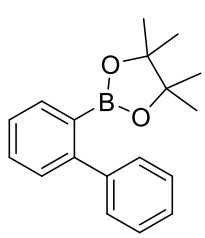
Colorless solid, yield: 60% (33.6 mg), melting point: 84-85 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.37 (s, 12H), 7.33-7.36 (m, 1H), 7.43-7.48 (m, 3H), 7.63-7.66 (m, 2H), 7.70-7.72 (m, 1H), 7.81-7.82 (m, 1H), 8.07 (s, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 25.0, 84.0, 127.3, 127.4, 128.3, 128.8, 130.1, 133.7, 133.8, 140.7, 141.3. (The signal for the carbon that is attached to the boron atom was not observed); $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 31.00.

4,4,5,5-Tetramethyl-2-(*o*-tolyl)-1,3,2-dioxaborolane (3n)[17]



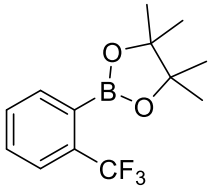
Colorless oil, yield: 38% (16.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.36 (s, 12H), 2.55 (s, 3H), 7.15-7.19 (m, 2H), 7.33 (td, J = 7.5, 1.5 Hz, 1H), 7.78 (dd, J = 7.5, 1.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 22.3, 25.0, 83.4, 124.8, 129.9, 130.9, 136.0, 144.9. (The signal for the carbon that is attached to the boron atom was not observed); $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 31.33.

2-([1,1'-Biphenyl]-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3o)[14]



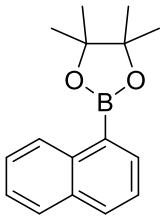
Colorless solid, yield: 78% (43.7 mg), melting point: 81-82 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (s, 12H), 7.32-7.42 (m, 7H), 7.44-7.47 (m, 1H), 7.71-7.74 (m, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 24.7, 83.9, 126.4, 127.0, 127.9, 129.1, 129.3, 130.2, 134.6, 143.4, 147.6. (The signal for the carbon that is attached to the boron atom was not observed); $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 31.73.

4,4,5,5-Tetramethyl-2-(2-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (3p)[17]



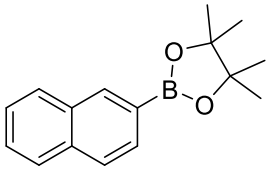
Colorless oil, yield: 49% (26.7 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.37 (s, 12H), 7.52-7.48 (m, 2H), 7.65-7.67 (m, 1H), 7.74-7.71 (m, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 24.8, 84.6, 124.2 (q, J = 272.1 Hz), 125.4 (q, J = 5.0 Hz), 130.1, 130.8, 134.1 (q, J = 32.6 Hz), 134.8. (The signal for the carbon that is attached to the boron atom was not observed); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -59.70; $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 31.17.

4,4,5,5-Tetramethyl-2-(naphthalen-1-yl)-1,3,2-dioxaborolane (3q)[14]



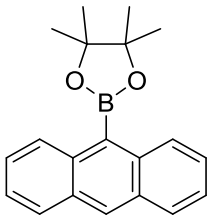
White solid, yield: 82% (41.7 mg), melting point: 54-55 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.43 (s, 12H), 7.46-7.48 (m, 2H), 7.53-7.55 (m, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.82-7.85 (m, 1H), 8.08 (d, J = 6.8 Hz, 1H), 8.75-8.79 (m, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 25.1, 83.9, 125.1, 125.6, 126.5, 128.5, 128.5, 131.7, 133.3, 135.8, 137.1. (The signal for the carbon that is attached to the boron atom was not observed); $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 31.52.

4,4,5,5-Tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane (3r)[17]



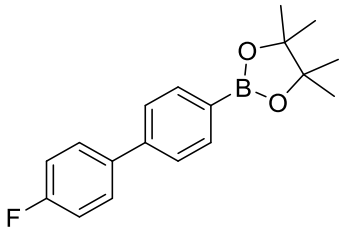
White solid, yield: 68% (34.6 mg), melting point: 62-63 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.40 (s, 12H), 7.47-7.53 (m, 2H), 7.82-7.88 (m, 3H), 7.88-7.92 (m, 1H), 8.39 (s, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 25.1, 84.1, 125.9, 127.1, 127.1, 127.8, 128.8, 130.5, 132.9, 135.1, 136.4. (The signal for the carbon that is attached to the boron atom was not observed); $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 31.14.

2-(Anthracen-9-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3s)[41]



Yellow solid, yield: 55% (33.5 mg), melting point: 134-135 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.59 (s, 12H), 7.45 (dd, J = 7.8, 6.5 Hz, 2H), 7.49 (dd, J = 8.7, 6.5 Hz, 2H), 8.00 (dd, J = 8.4, 1.5 Hz, 2H), 8.44-8.49 (m, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 25.3, 84.5, 125.0, 125.9, 128.4, 128.9, 129.6, 131.3, 136.0. (The signal for the carbon that is attached to the boron atom was not observed); $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 32.96.

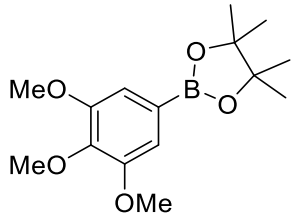
2-(4'-Fluoro-[1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3t)[42]



White solid, yield: 71% (42.5 mg), melting point: 115-116 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.37 (s, 12H), 7.11-7.15 (m, 2H), 7.55-7.59 (m, 4H), 7.87-7.90 (m, 2H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 25.0, 84.0, 115.8 (d, J = 21.4 Hz), 126.4, 128.9 (d, J = 8.1 Hz), 135.4, 137.2 (d, J = 3.3 Hz), 143.0, 162.8 (d, J = 246.8 Hz). (The signal for the carbon

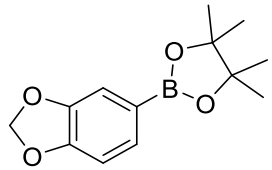
that is attached to the boron atom was not observed); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -115.31; $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 30.85.

4,4,5,5-Tetramethyl-2-(3,4,5-trimethoxyphenyl)-1,3,2-dioxaborolane (3u)[43]



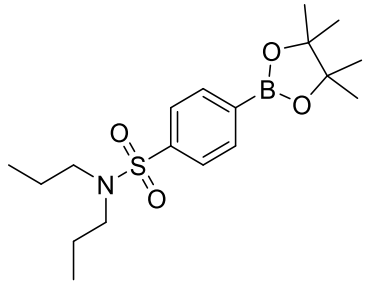
Colorless solid, yield: 50% (29.4 mg), melting point: 105-106 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (s, 12H), 3.87 (s, 3H), 3.90 (s, 6H), 7.03 (s, 2H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 25.0, 56.3, 60.9, 84.0, 111.4, 140.9, 153.0. (The signal for the carbon that is attached to the boron atom was not observed); $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 30.64.

2-(Benzo[d][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3v)[14]



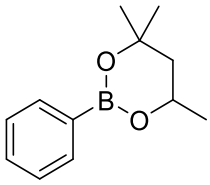
Colorless oil, yield: 75% (37.2 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (s, 12H), 5.95 (s, 2H), 6.83 (d, J = 7.7 Hz, 1H), 7.24 (d, J = 1.1 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 25.0, 83.8, 100.9, 108.4, 114.1, 129.8, 147.3, 150.3. (The signal for the carbon that is attached to the boron atom was not observed); $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 30.57.

***N,N*-Dipropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (3w)**[17]



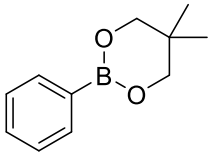
White solid, yield: 74% (54.4 mg), melting point: 149-150 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.85 (t, J = 7.4 Hz, 3H), 1.35 (s, 6H), 1.48-1.57 (m, 2H), 3.02-3.09 (m, 2H), 7.78 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 11.3, 22.1, 25.0, 50.1, 84.5, 126.1, 135.3, 142.5. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 30.43.

4,4,6-Trimethyl-2-phenyl-1,3,2-dioxaborinane (4b)[44]



Colorless oil, yield: 54% (22.0 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.45-1.40 (m, 9H), 1.64 (dd, J = 13.8, 11.5 Hz, 1H), 1.90 (dd, J = 13.8, 3.0 Hz, 1H), 4.39 (ddq, J = 12.3, 6.2, 3.1 Hz, 1H), 7.38-7.42 (m, 2H), 7.44-7.48 (m, 1H), 7.90 (dd, J = 8.1, 1.5 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 23.3, 28.3, 31.4, 46.1, 65.0, 71.0, 127.5, 130.4, 133.9. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 26.80.

5,5-Dimethyl-2-phenyl-1,3,2-dioxaborinane (4c)[11]

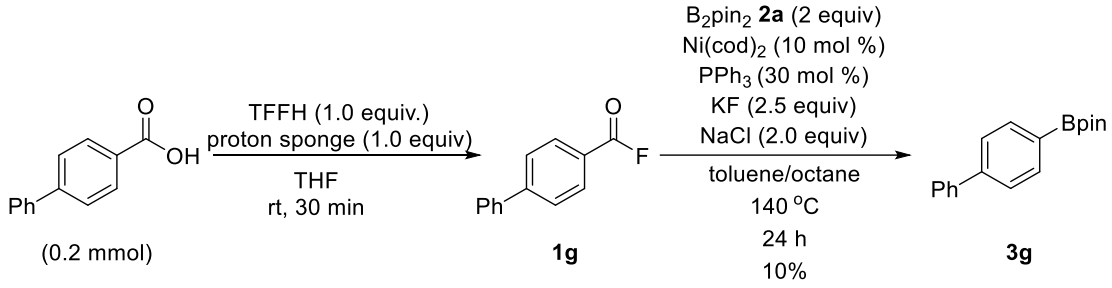


Colorless oil, yield: 55% (20.9 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.03 (s, 6H), 3.78 (s, 4H), 7.37 (d, J = 8.2 Hz, 2H), 7.41-7.46 (m, 1H), 7.82 (d, J = 7.9 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 22.1, 32.0, 72.5, 127.7, 130.8, 134.0. (The signal for the carbon that is attached to the boron atom was not observed); ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$) δ 26.84.

3-4-2-4 One-pot Synthesis from Carboxylic Acid without Isolation of Aroyl Fluorides

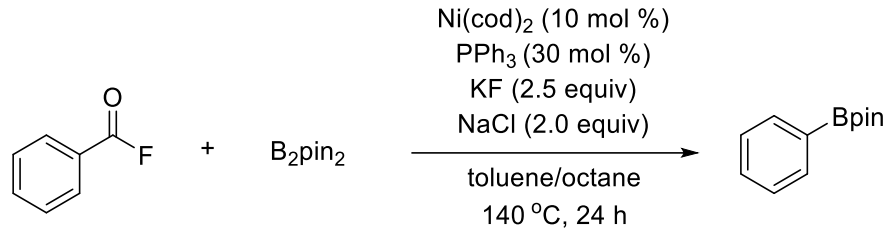
To a 20 mL of Schlenk tube charged with a magnetic stirrer bar, were successively added [1,1'-biphenyl]-4-carboxylic acid (39.6 mg, 0.2 mmol) and TFFH (52.8 mg, 0.2 mmol, 1.0

equiv), proton sponge (42.9 mg, 0.2 mmol, 1.0 equiv), and THF (0.4 mL). After the reaction mixture was stirred at room temperature for 15 to 30 min, a pre-mixed solution of $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 10 mol %), PPh_3 (15.7 mg, 0.06 mmol, 30 mol %) in toluene (0.66 mL) and octane (0.33 mL) was added. Then, KF (30.6 mg, 0.5 mmol, 2.5 equiv), bis(pinacolato)diboron (**2a**) (101.6 mg, 0.6 mmol, 2.0 equiv), and NaCl (23.4 mg, 0.6 mmol, 2.0 equiv) were added. The mixture was heated at 140 ºC with stirring for 24 h. After the reaction, *n*-dodecane was added as an internal standard and stirring the mixture vigorously. Take a portion of the mixture, diluted by Et_2O (2 mL), GC analysis was measured to evident the formation of **3g** in 10%.



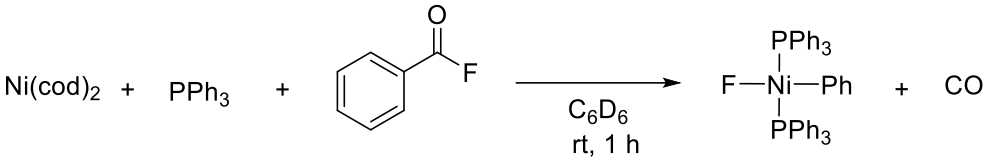
3-4-2-5 Gram-scale Experiment

An oven-dried two necked flask (100 mL) containing a stirring bar was charged with $Ni(cod)_2$ (275 mg, 1.0 mmol, 10 mol %), PPh_3 (785 mg, 3.0 mmol, 30 mol %), toluene (33 mL), octane (16.5 mL) and stirring for 1 min at room temperature. Then, benzoyl fluoride (**1a**) (10 mmol, 1.07 mL), KF (1.53 g, 25 mmol, 2.5 equiv), bis(pinacolato)diboron (**2a**) (5.08 g, 20 mmol, 2.0 equiv), and NaCl (1.17 g, 20 mmol, 2.0 equiv) were added. The mixture was heated at 140 ºC with stirring for 24 h. After cooling to room temperature, to the mixture were added saturated aqueous ammonium chloride (ca. 50 mL) and extracted with EtOAc (ca. 50 mL × 3), successively. The combined organic extracts were dried over Na_2SO_4, and then filtrated. The filtrate was concentrated under reduced pressure to give the residue, which was purified by column chromatography on silica gel to afford **3a** (1.19 g, 58%).

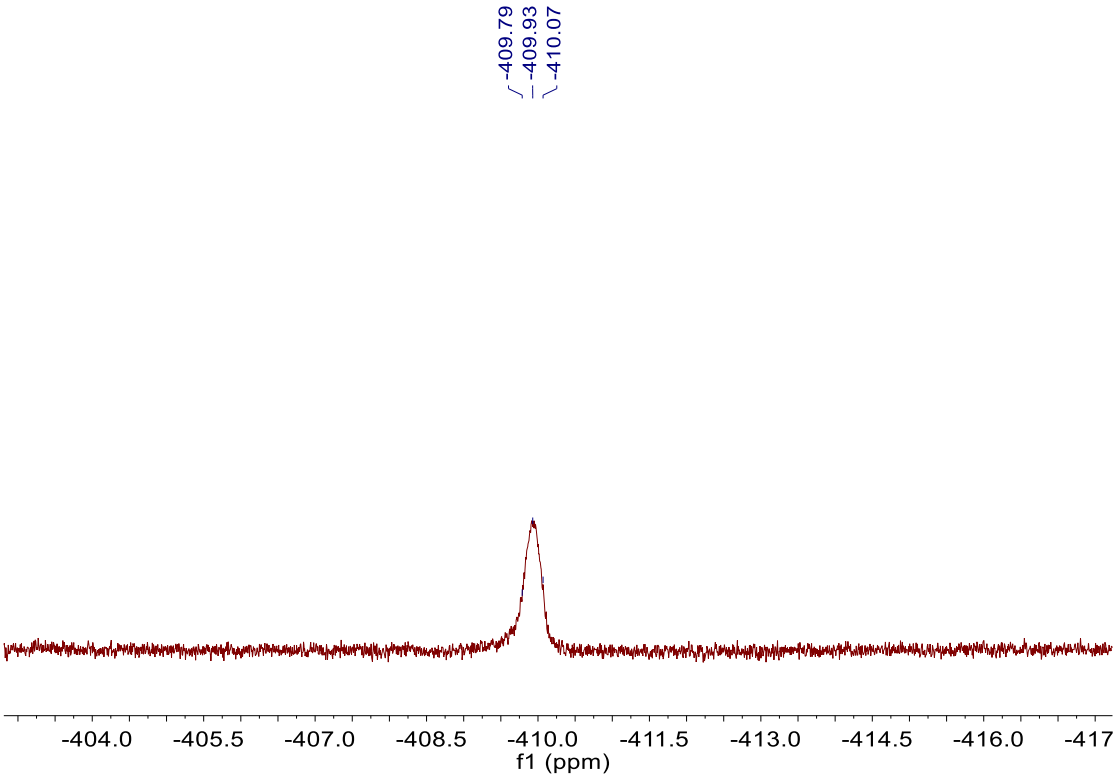


1a (10 mmol) **2a** (2 equiv) **3a,** 58% (1.19 g)

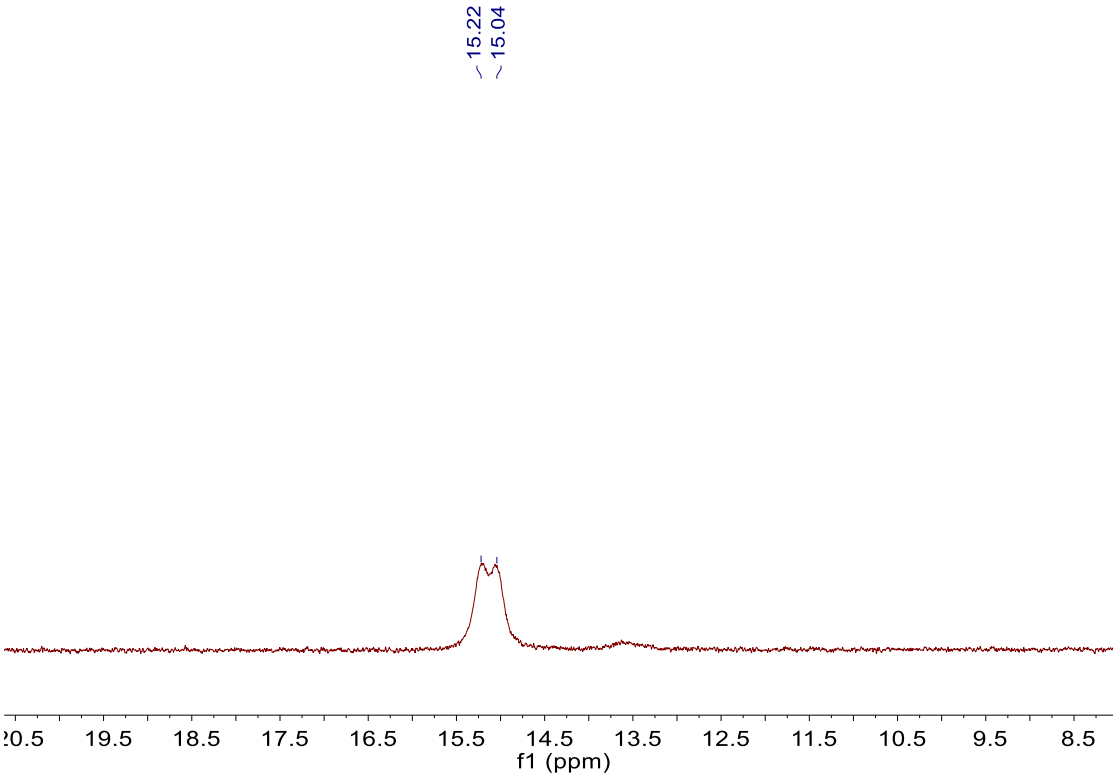
3-4-2-6 Elucidation of the Isolation of Oxidative Adduct



An oven dried Schlenk tube containing a stirring bar was charged with $Ni(cod)_2$ (13.7 mg, 0.03 mmol,), PPh_3 (26.2 mg, 0.1 mmol), C_6D_6 (0.66 mL) and stirring for 30 seconds at room temperature. The resulting dark red solution was transferred to an NMR tube. Then, benzoyl fluoride (660 μL, 0.03 mmol) was added, the solution rapidly changed from a dark red to a bright orange. After 5 min, the $^{19}F\{^1H\}$ NMR was measured.

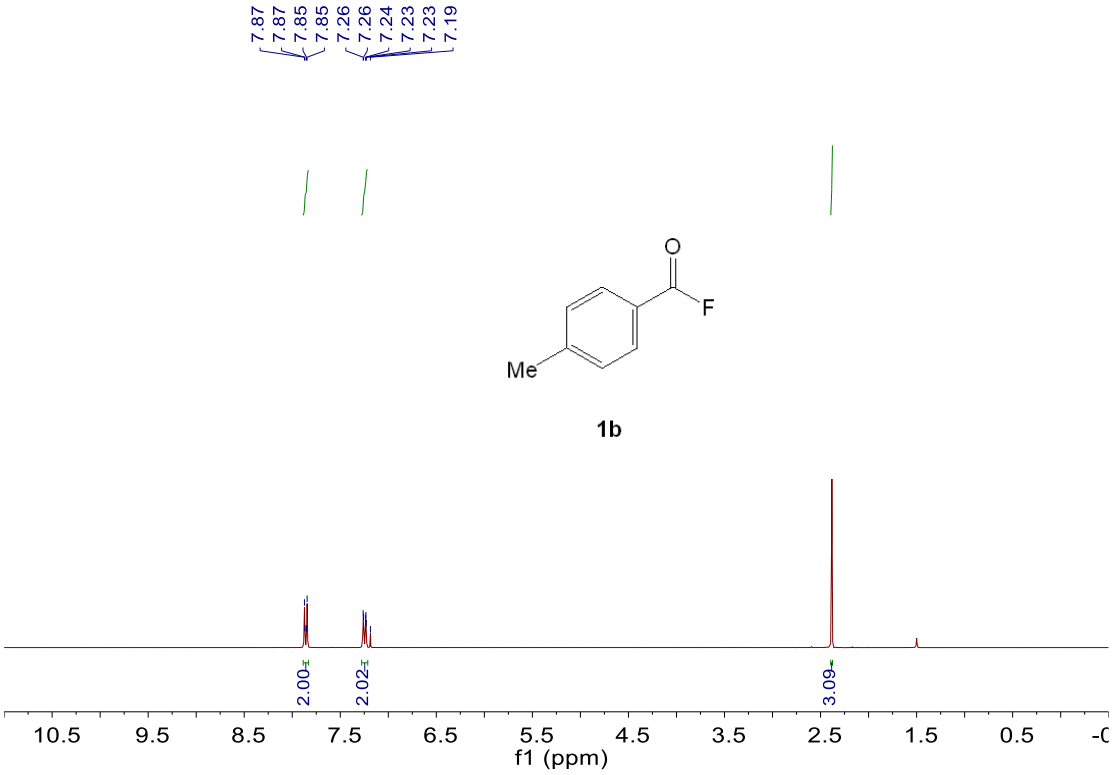


$^{19}F\{^1H\}$ NMR (376 MHz, C_6D_6) spectrum of the reaction mixture (C_6D_6, rt, 1 h).

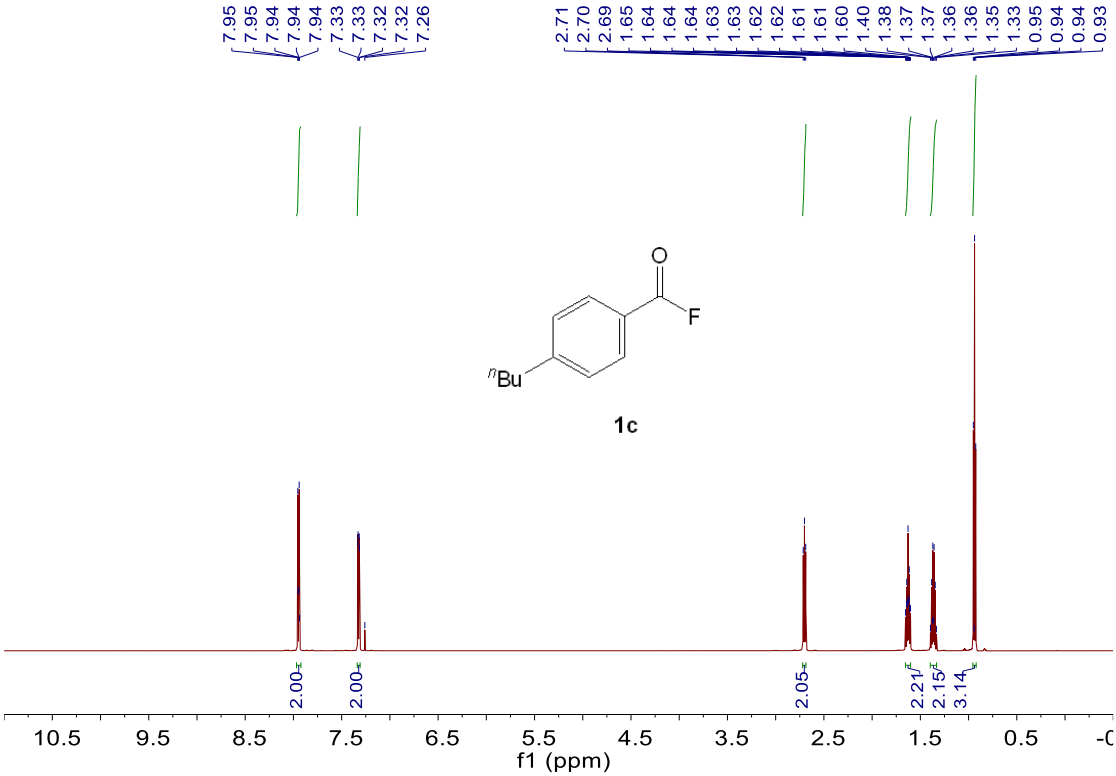


$^{31}P\{^{1}H\}$ NMR (243 MHz) spectrum of the reaction mixture (C_6D_6, rt, 1 h).

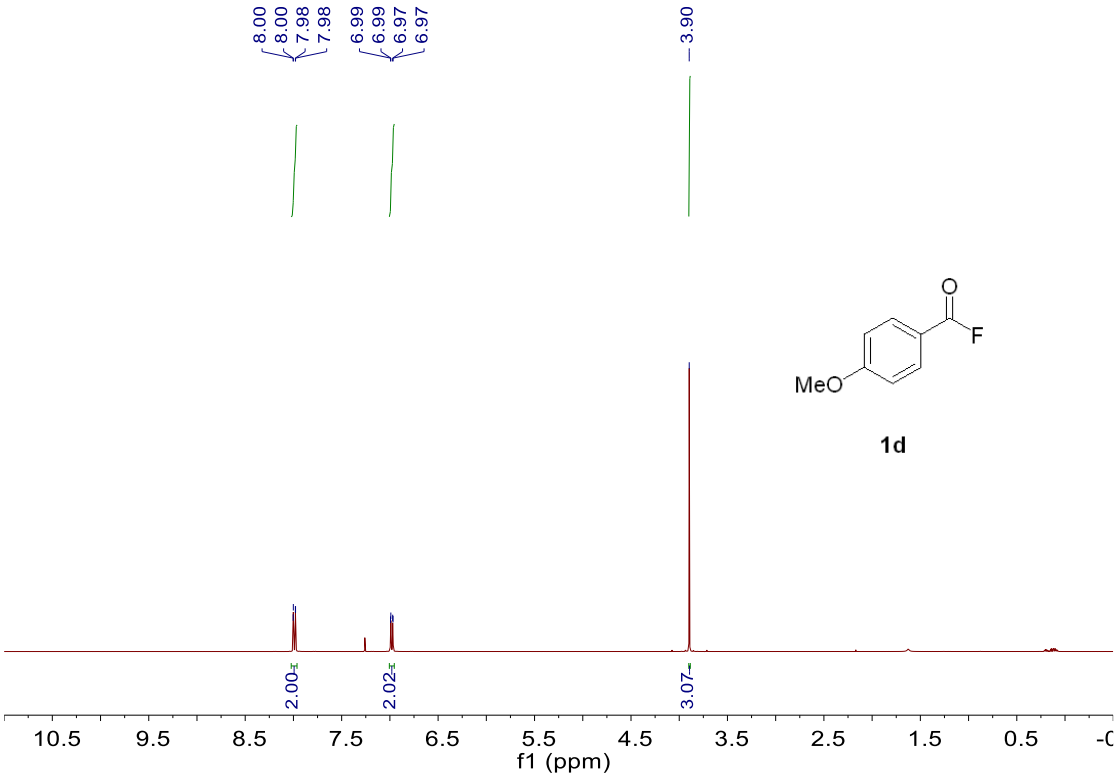
3-4-3 Copies of ^{1}H, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$ and $^{11}B\{^{1}H\}$ and NMR Charts



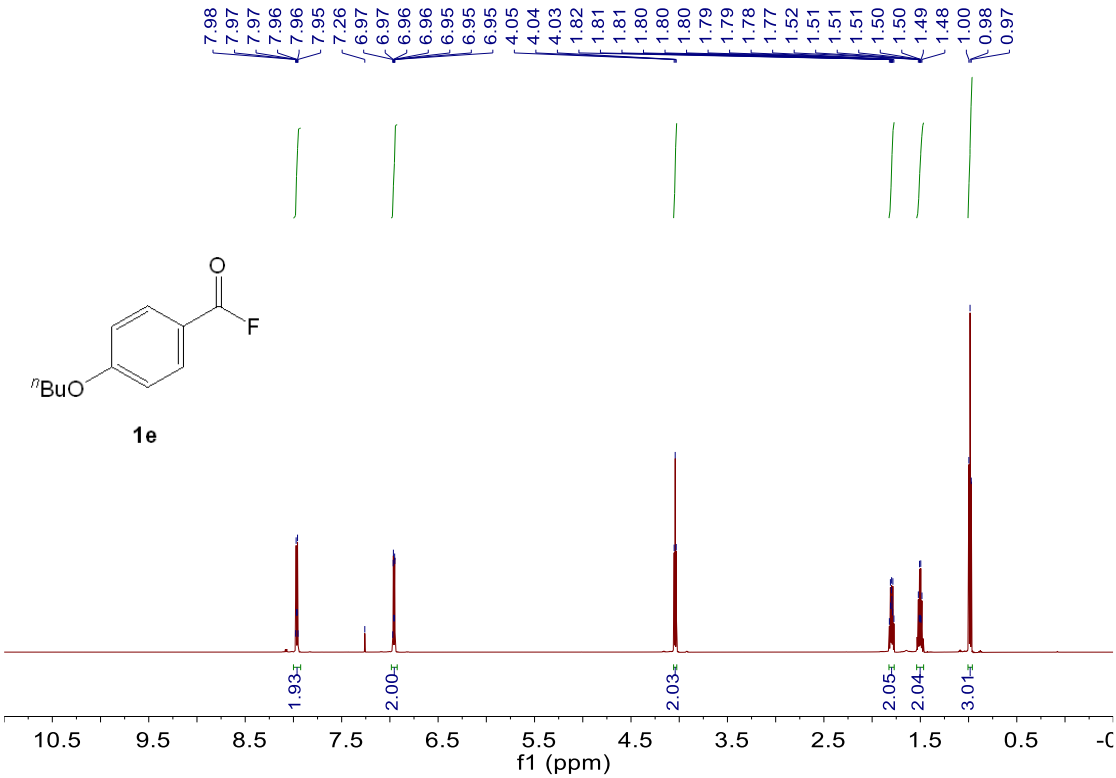
^{1}H NMR (300 MHz) spectrum of **1b** ($CDCl_3$, rt).



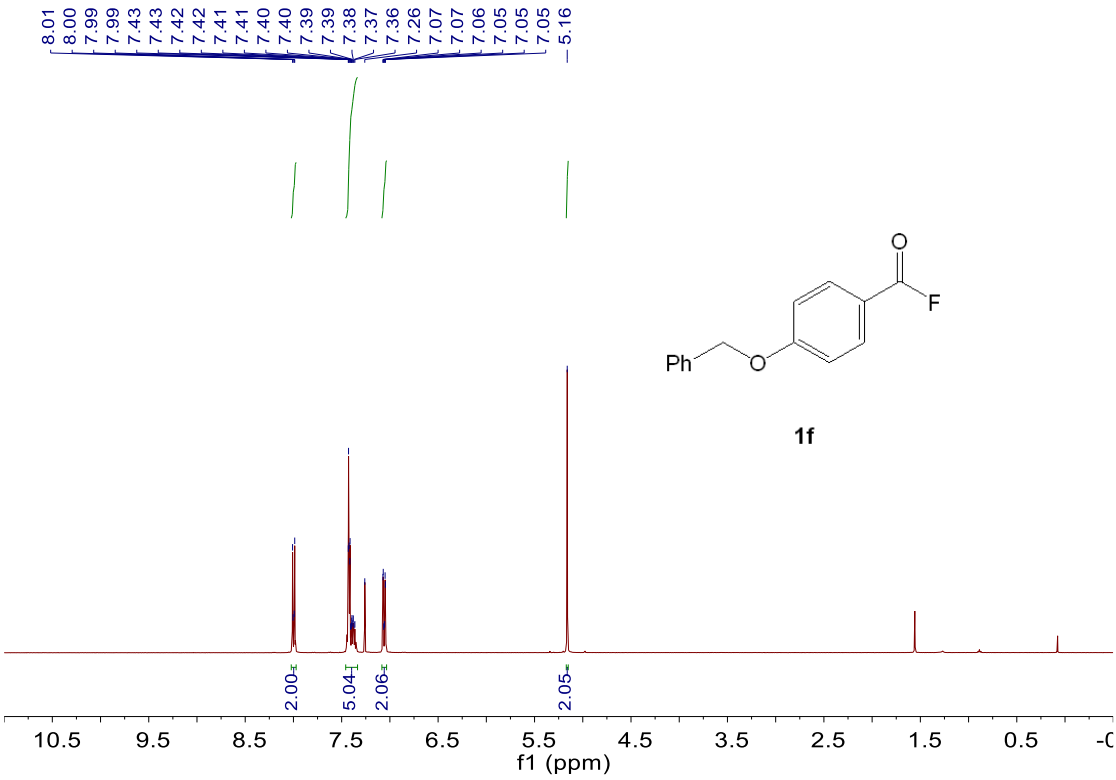
^{1}H NMR (600 MHz) spectrum of **1c** ($CDCl_3$, rt).

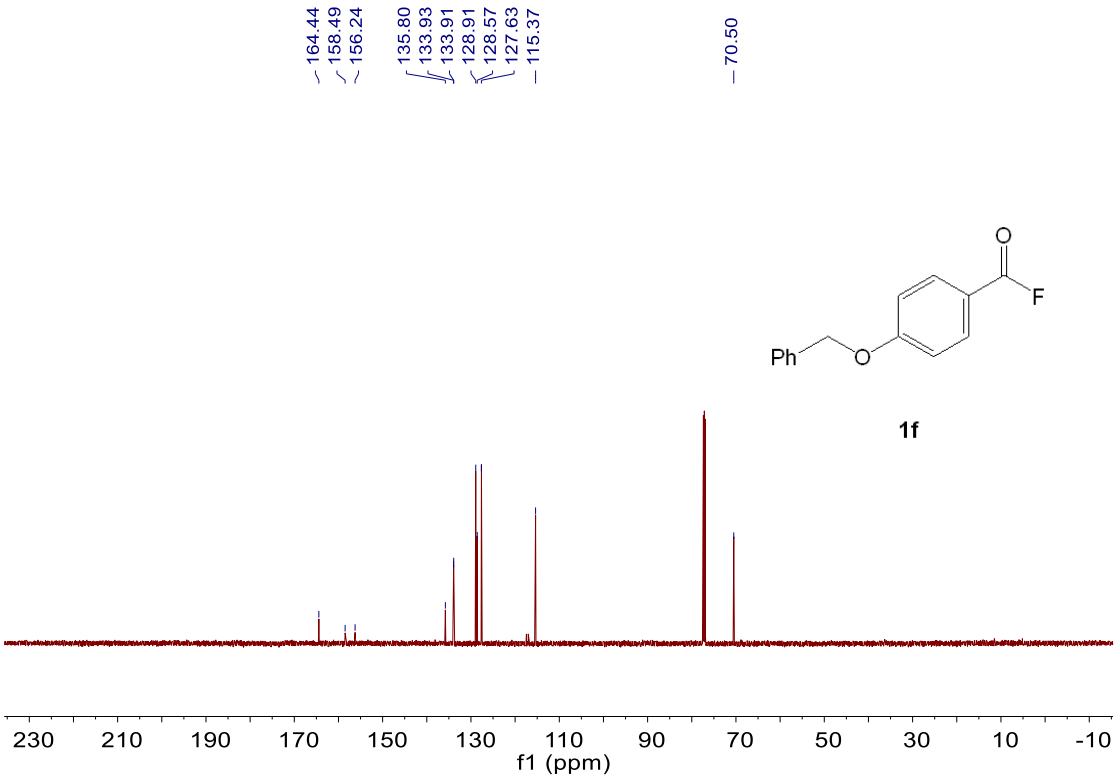


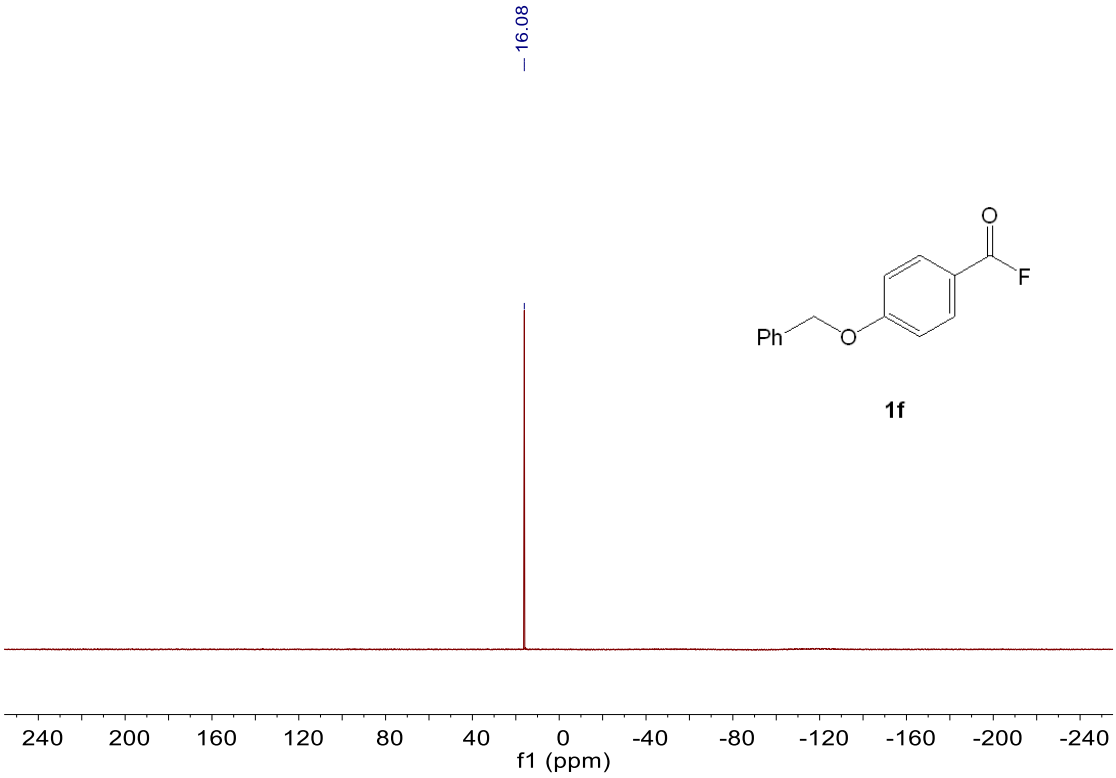
^{1}H NMR (400 MHz) spectrum of **1d** ($CDCl_3$, rt).



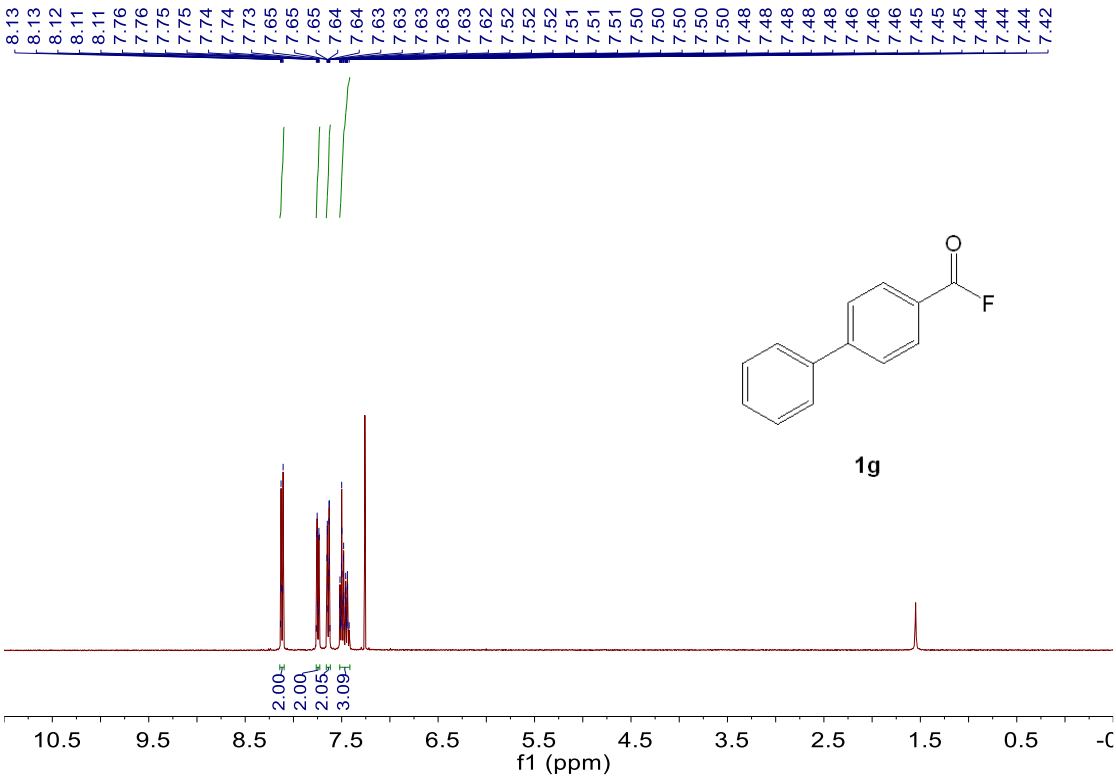
^{1}H NMR (600 MHz) spectrum of **1e** ($CDCl_3$, rt).


8.01
8.00
7.99
7.99
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.38
7.37
7.36
7.26
7.07
7.07
7.06
7.05
7.05
7.05
5.16
O
F
Ph
O
1f
2.00
5.04
2.06
2.05
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

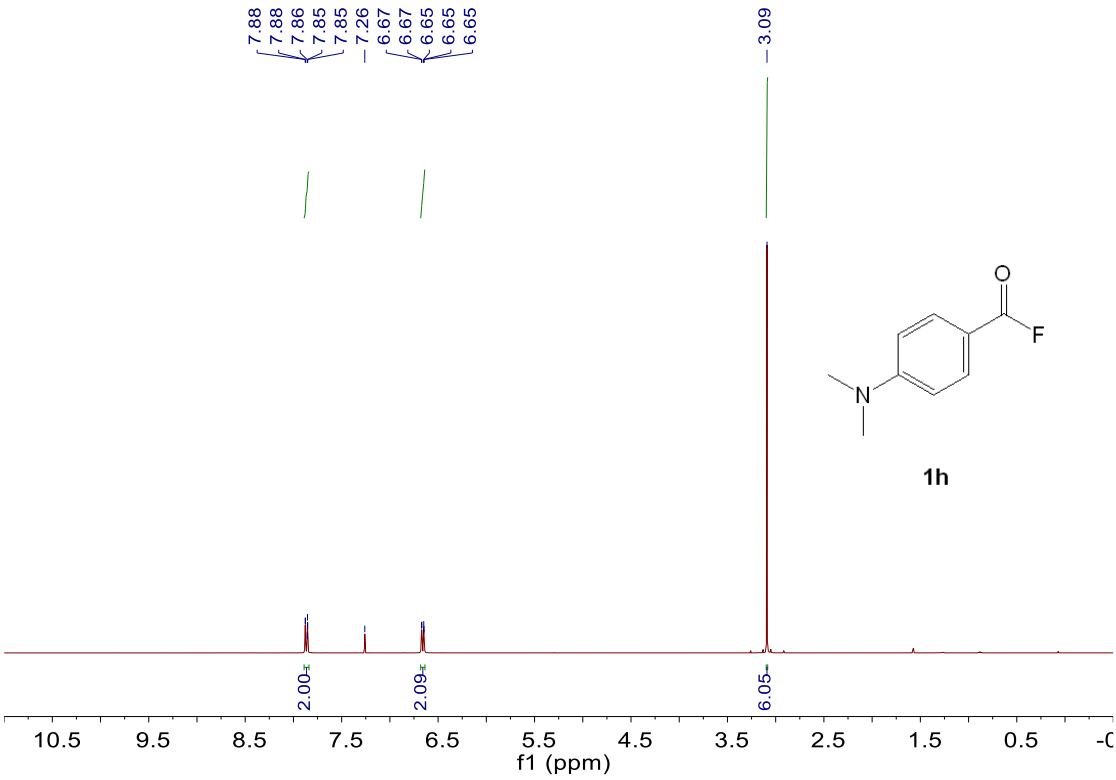

164.44
158.49
156.24
135.80
133.93
133.91
128.91
128.57
127.63
115.37
70.50
O
F
Ph
O
1f
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)



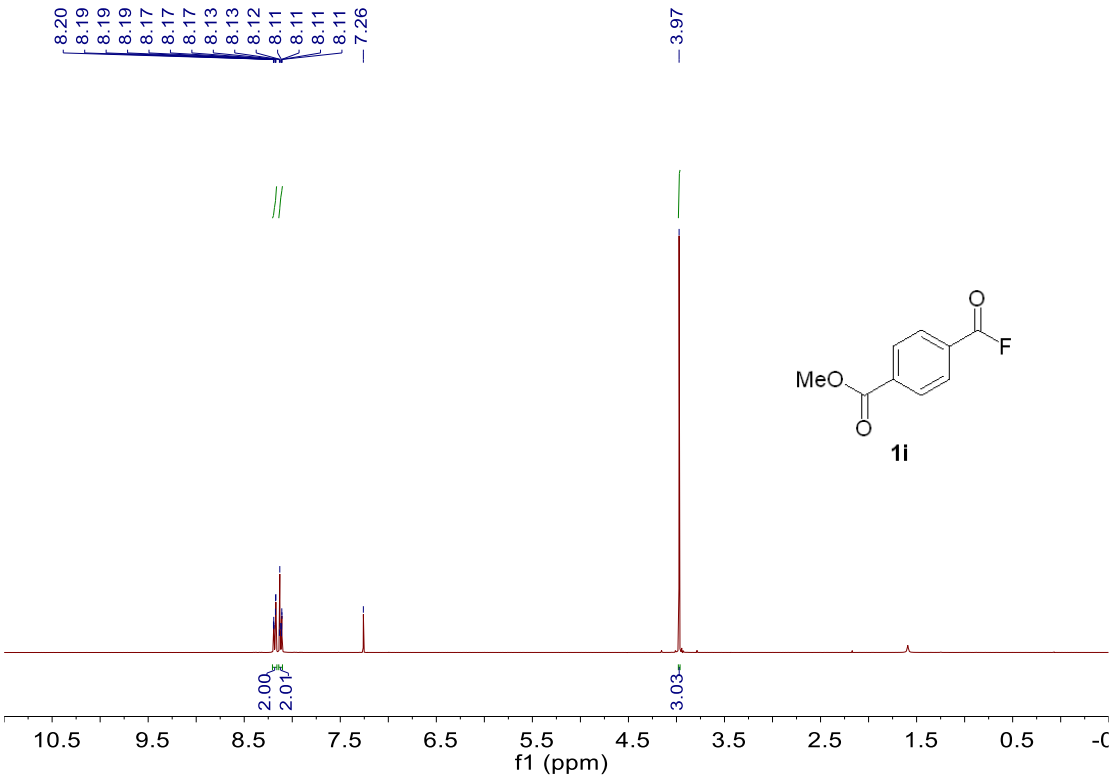
^{1}H NMR (400 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{19}F{^{1}H} NMR (376 MHz) spectra of **1f** ($CDCl_3$, rt).



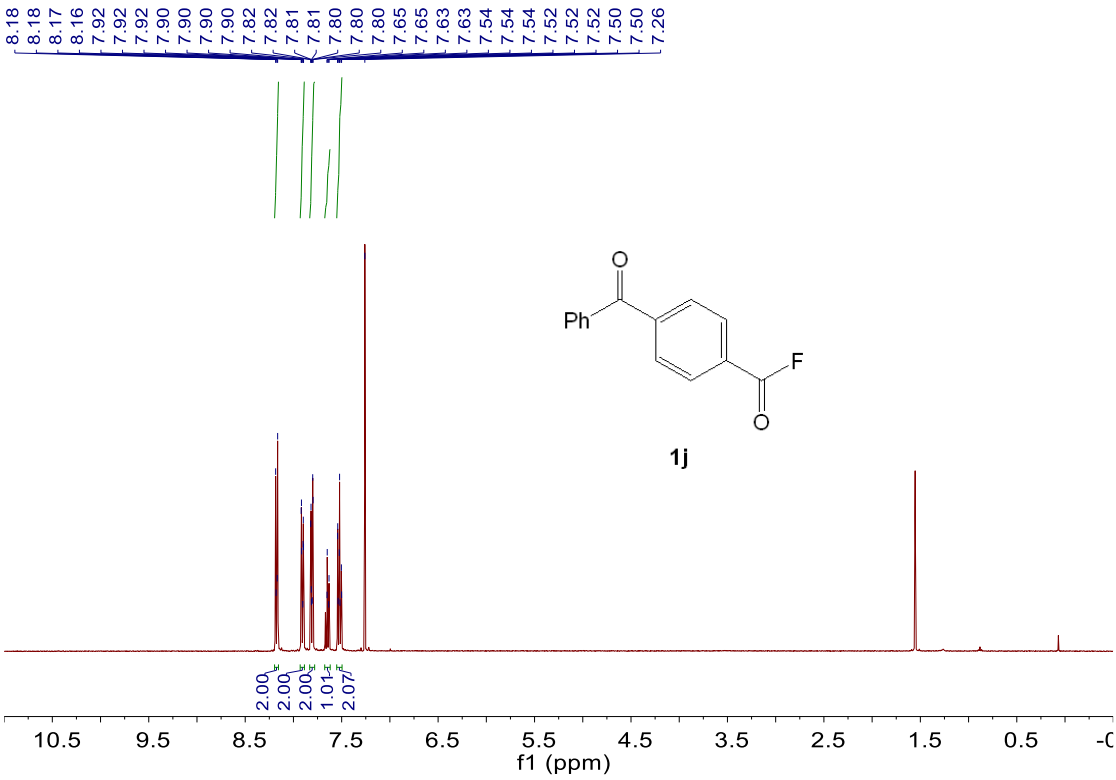
^{1}H NMR (400 MHz) spectrum of **1g** ($CDCl_3$, rt).

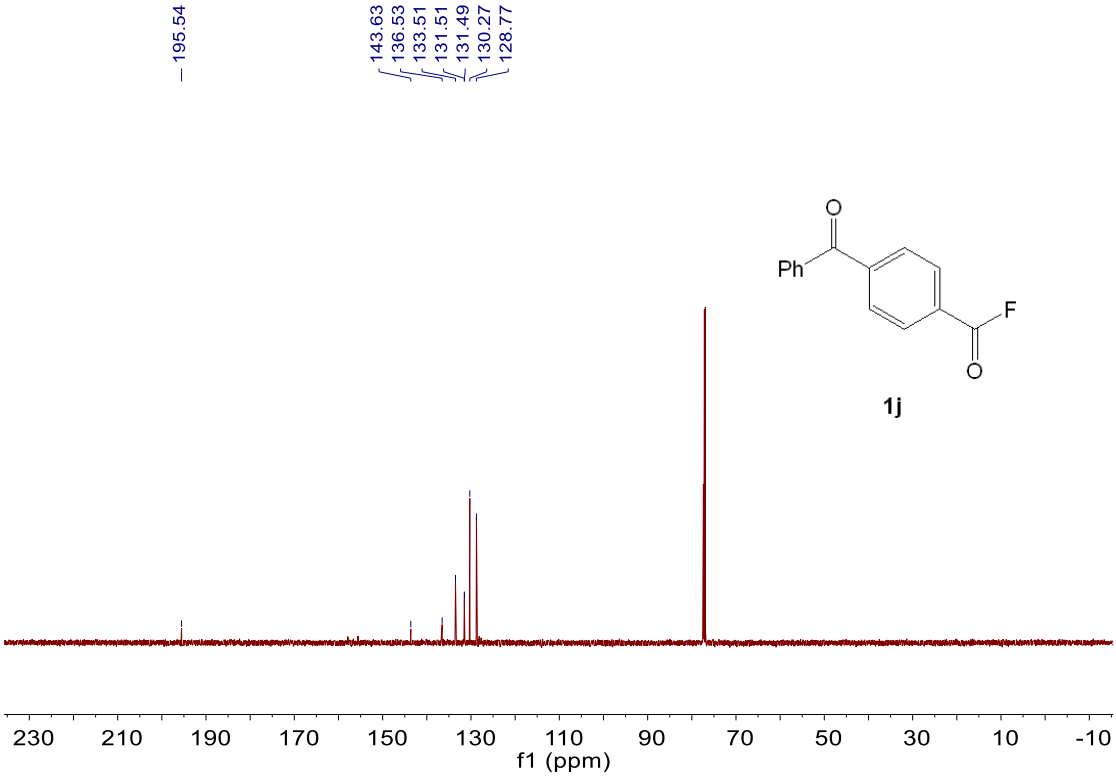


^{1}H NMR (400 MHz) spectrum of **1h** ($CDCl_3$, rt).



^{1}H NMR (400 MHz) spectrum of **1i** ($CDCl_3$, rt).


8.18
8.18
8.17
8.16
7.92
7.92
7.92
7.90
7.90
7.90
7.90
7.90
7.82
7.82
7.81
7.81
7.80
7.80
7.80
7.65
7.65
7.63
7.63
7.54
7.54
7.52
7.52
7.52
7.50
7.50
7.26
O
Ph
F
O
1j
2.00
2.00
2.00
1.01
2.07
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


195.54
143.63
136.53
133.51
131.51
131.49
130.27
128.77
O
Ph
F
O
1j
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170
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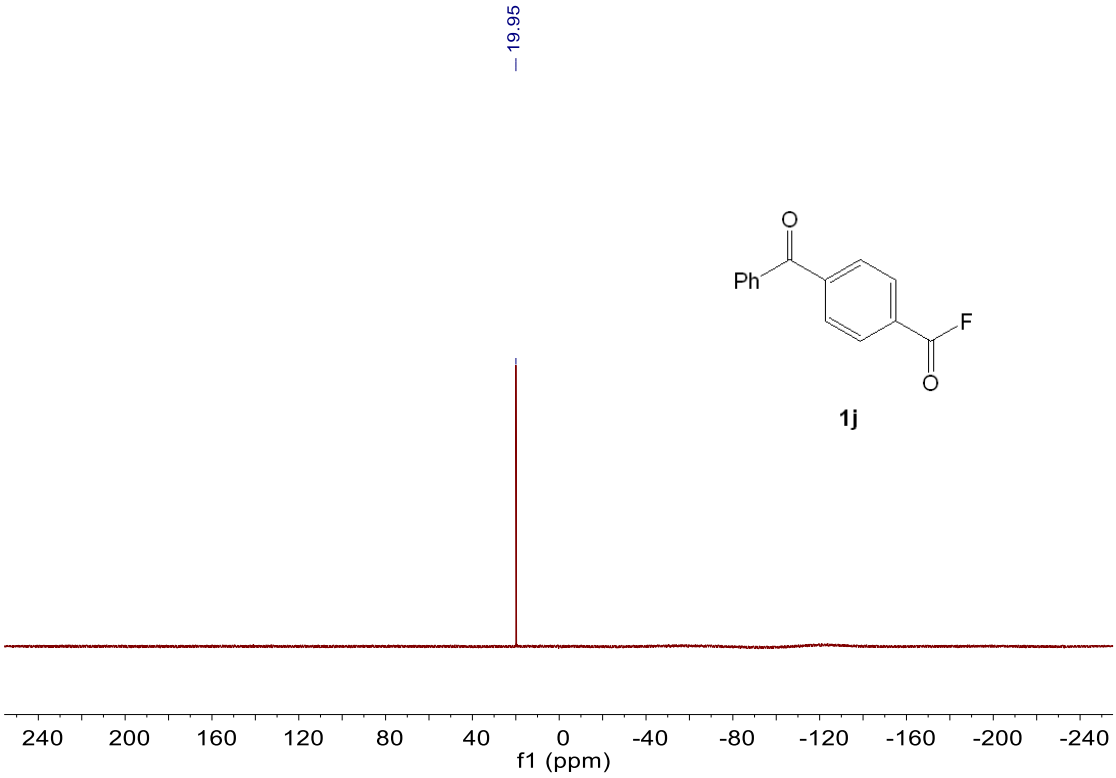
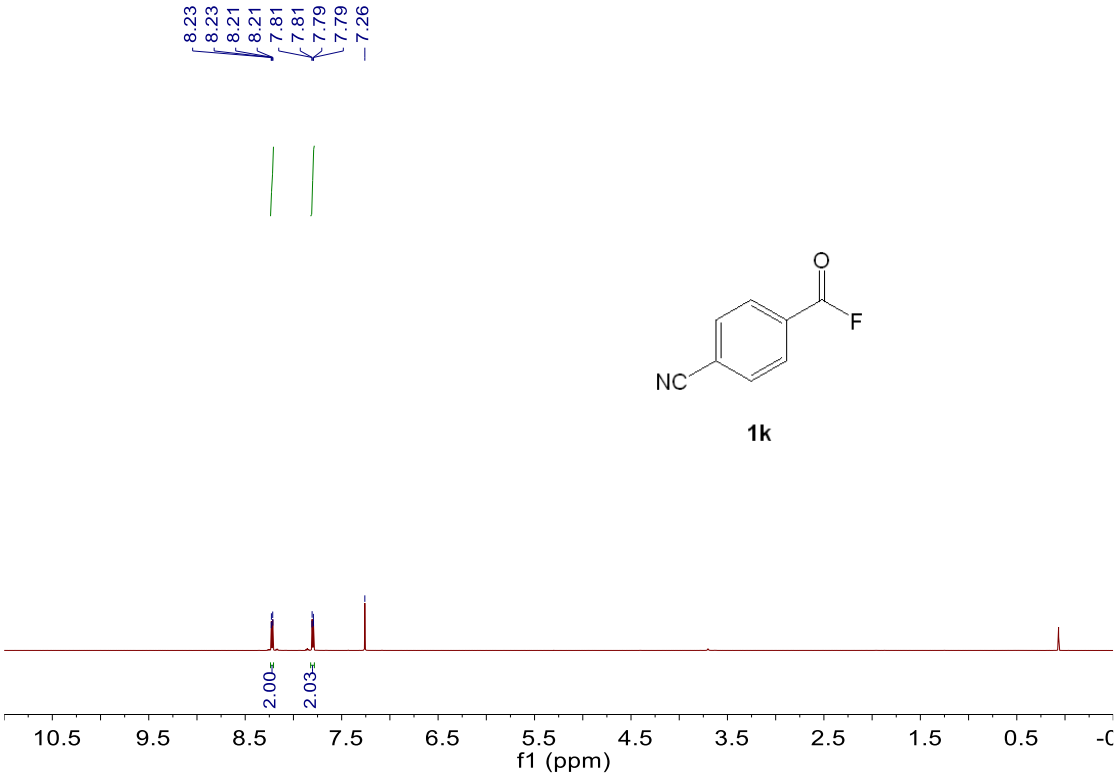
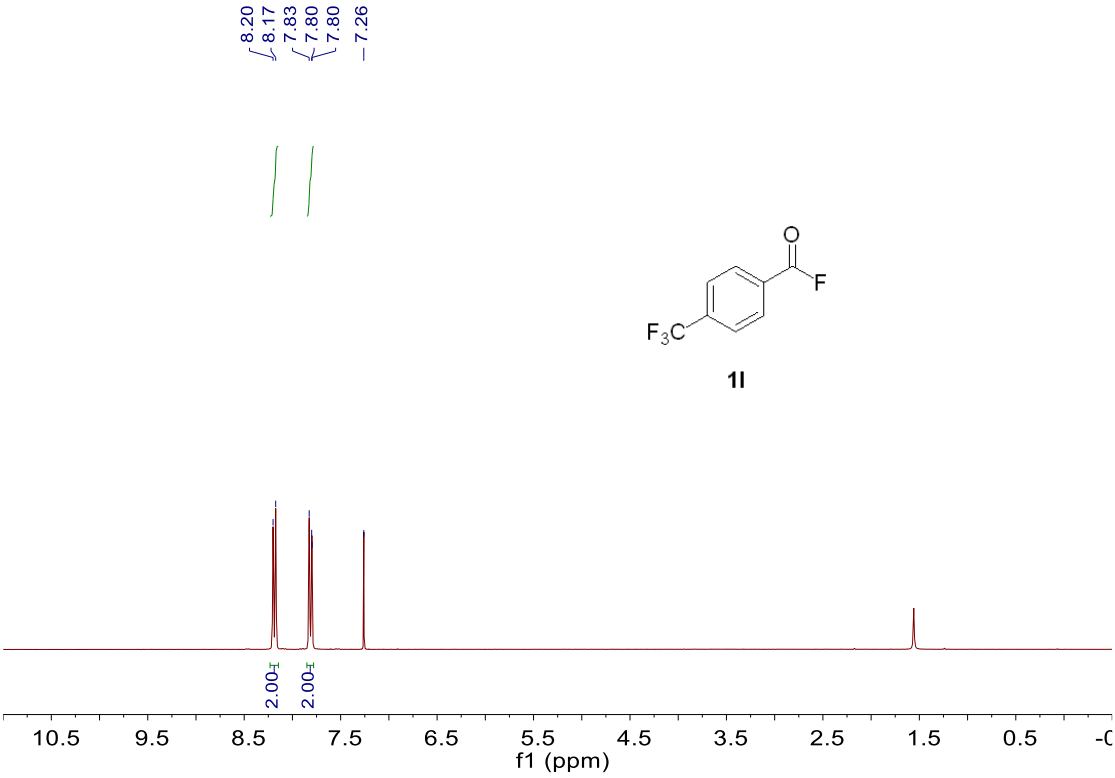
130
110
90
70
50
30
10
-10
f1 (ppm)



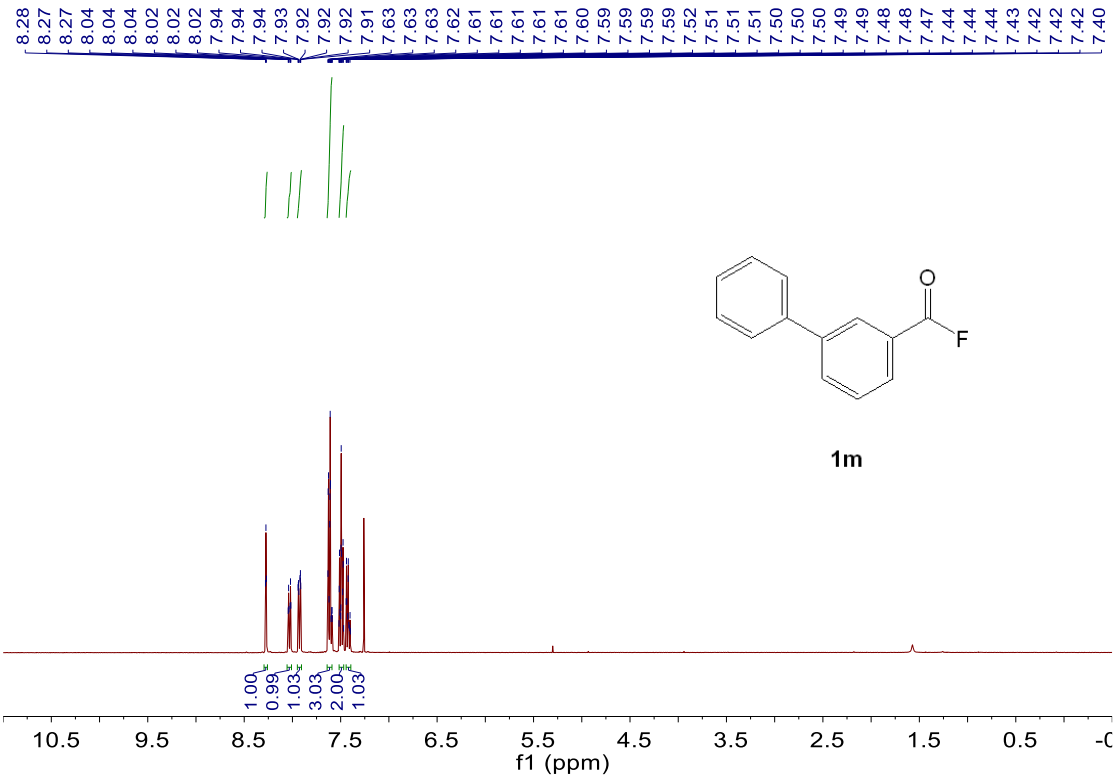
^{1}H NMR (400 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{19}F{^{1}H} NMR (376 MHz) spectra of **1j** ($CDCl_3$, rt).



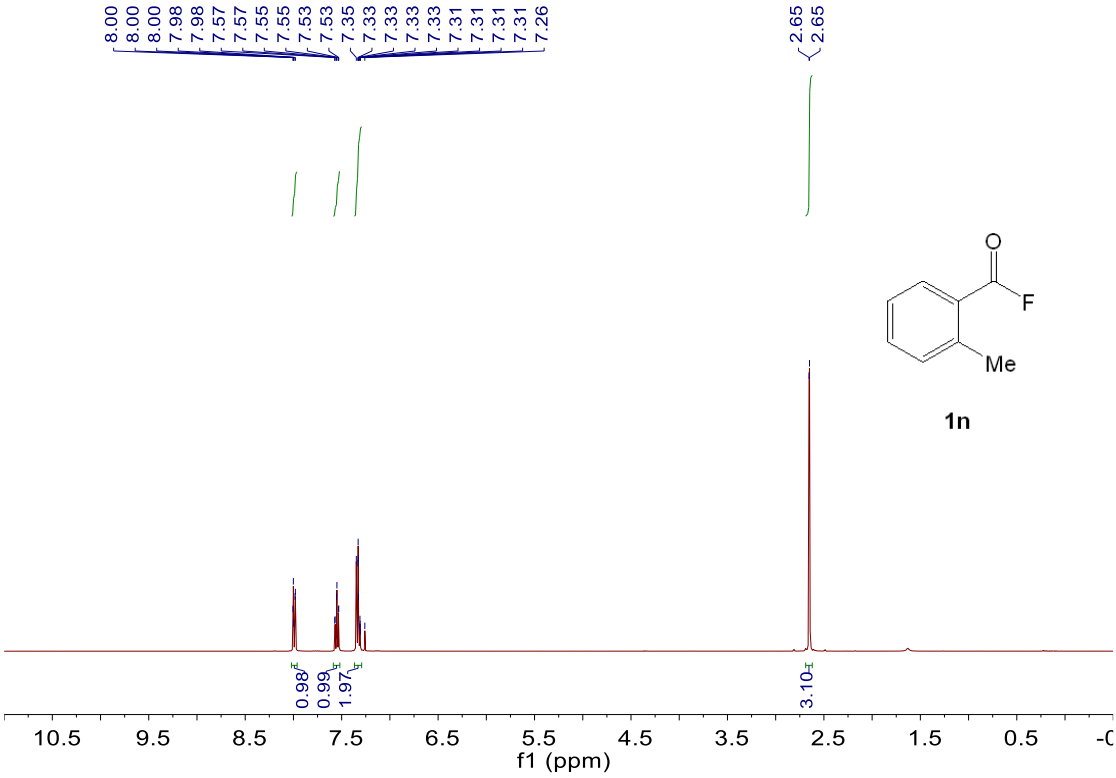
^{1}H NMR (600 MHz) spectrum of **1k** ($CDCl_3$, rt).



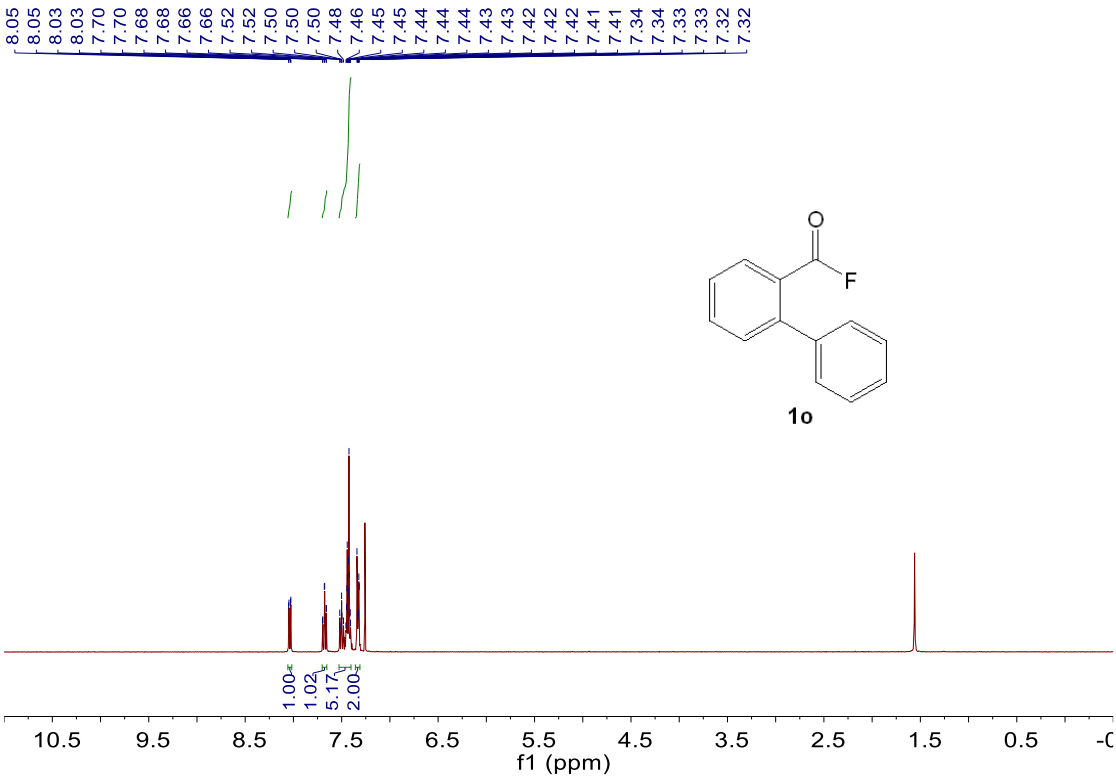
^{1}H NMR (300 MHz) spectrum of **1l** ($CDCl_3$, rt).



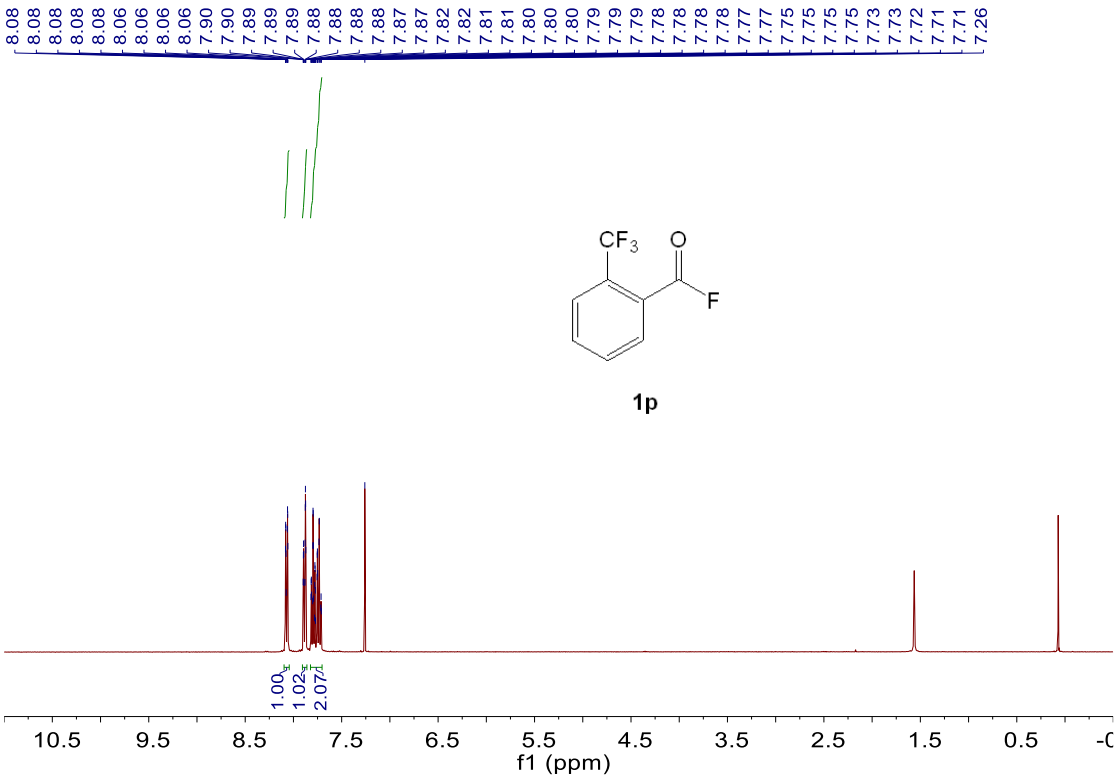
^{1}H NMR (400 MHz) spectrum of **1m** ($CDCl_3$, rt).



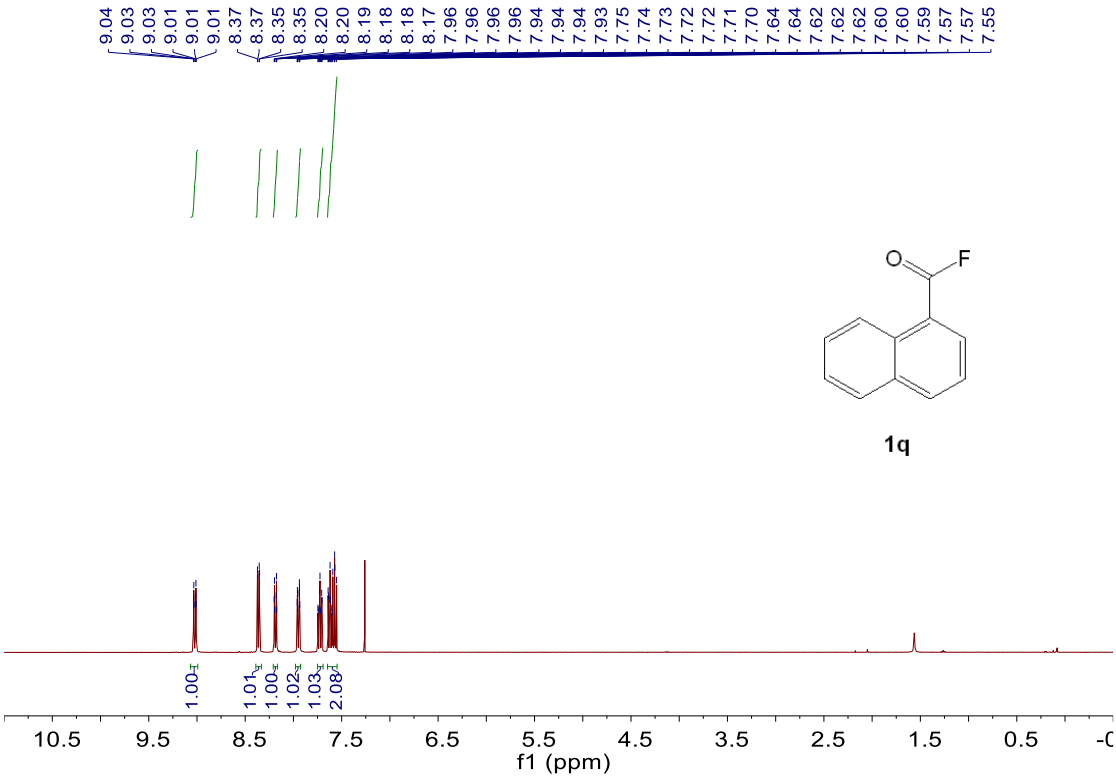
^{1}H NMR (400 MHz) spectrum of **1n** ($CDCl_3$, rt).



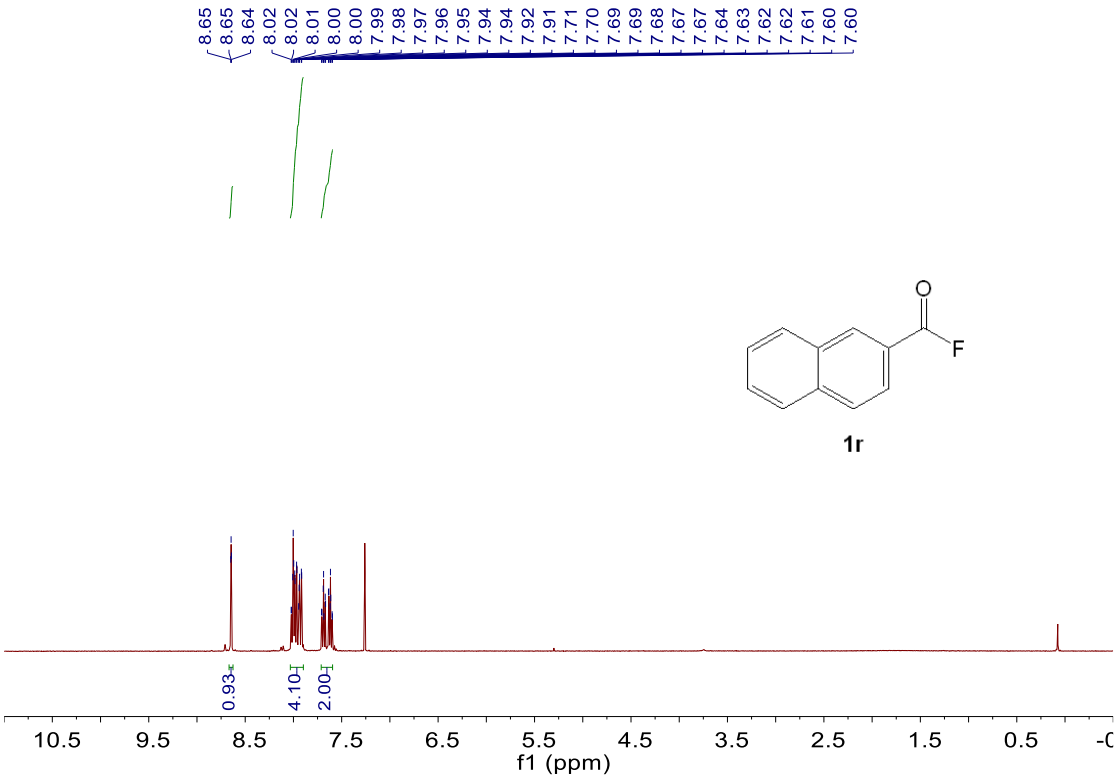
^{1}H NMR (400 MHz) spectrum of **1o** ($CDCl_3$, rt).



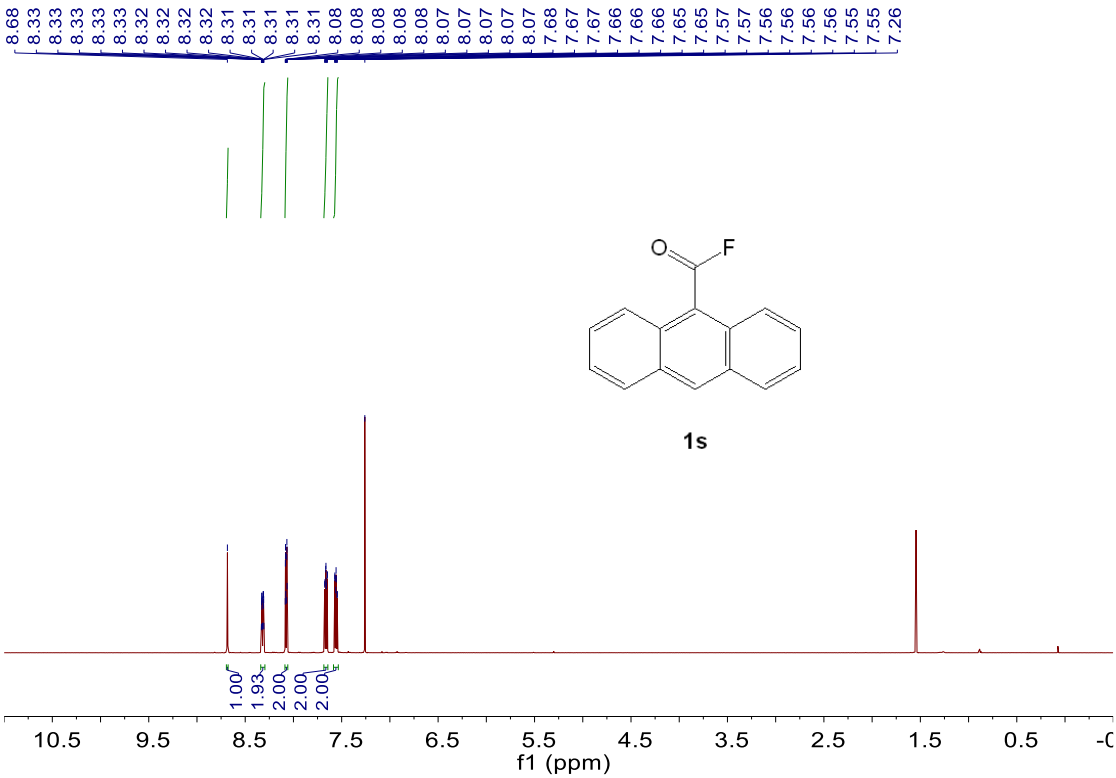
^{1}H NMR (400 MHz) spectrum of **1p** ($CDCl_3$, rt).



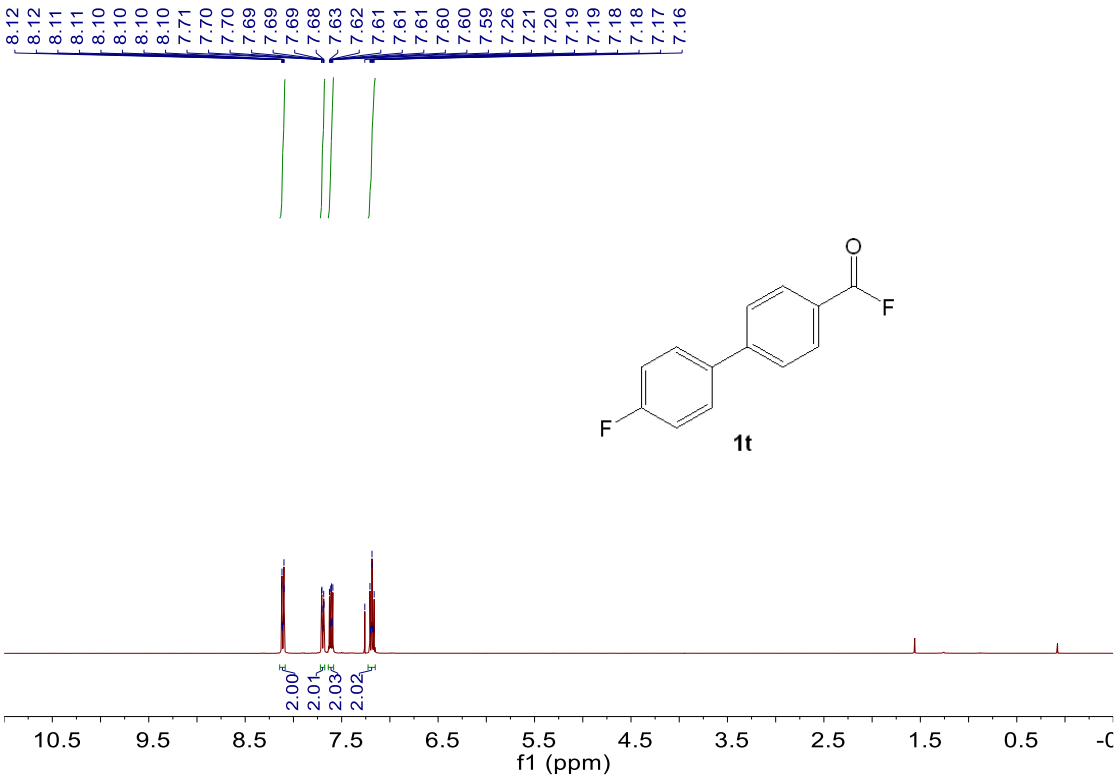
^{1}H NMR (400 MHz) spectrum of **1q** ($CDCl_3$, rt).



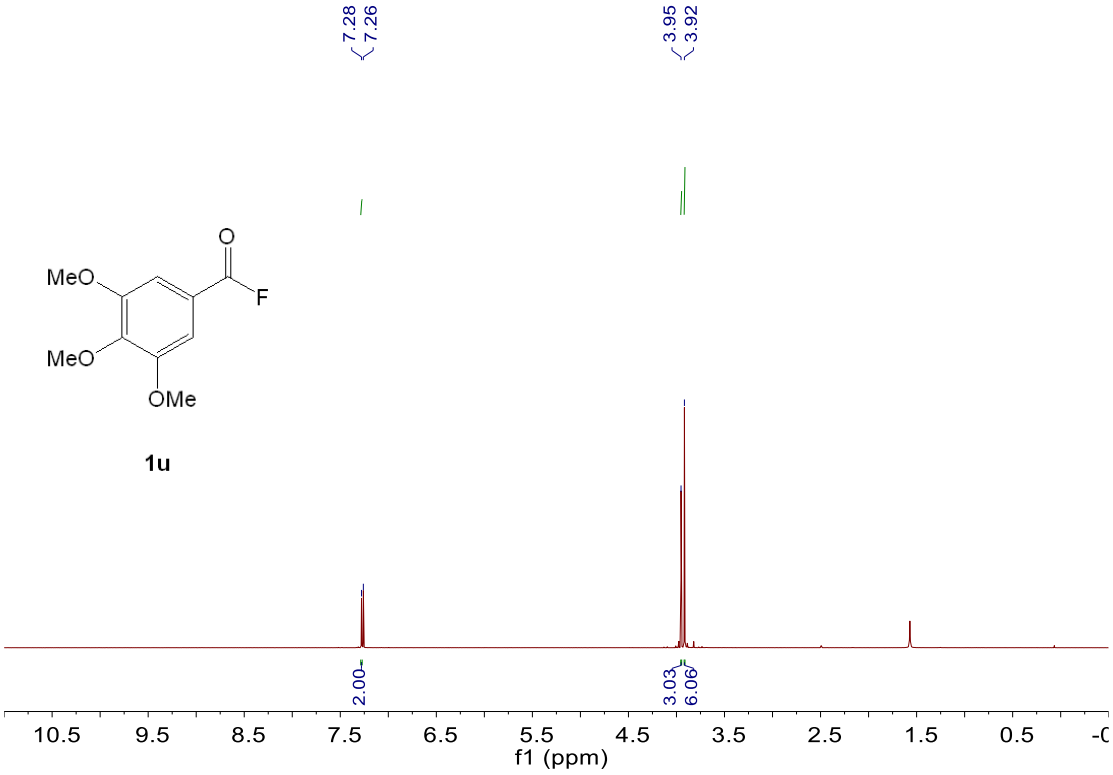
^{1}H NMR (400 MHz) spectrum of **1r** ($CDCl_3$, rt).



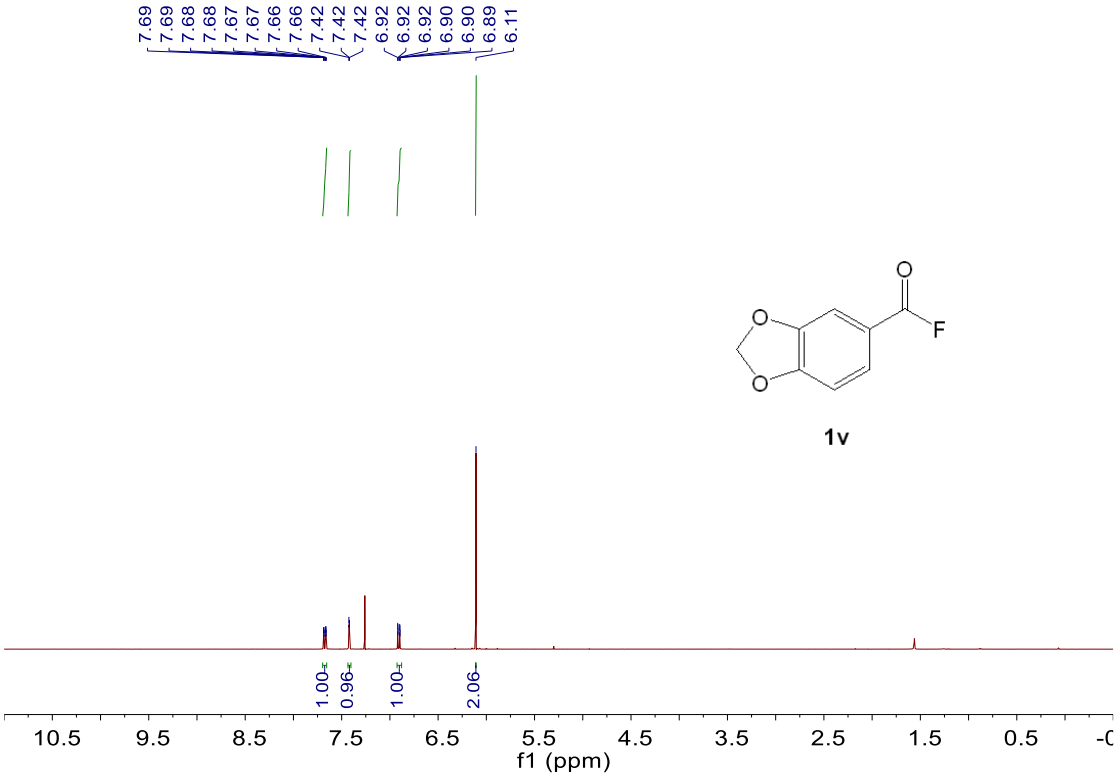
^{1}H NMR (600 MHz) spectrum of **1s** ($CDCl_3$, rt).

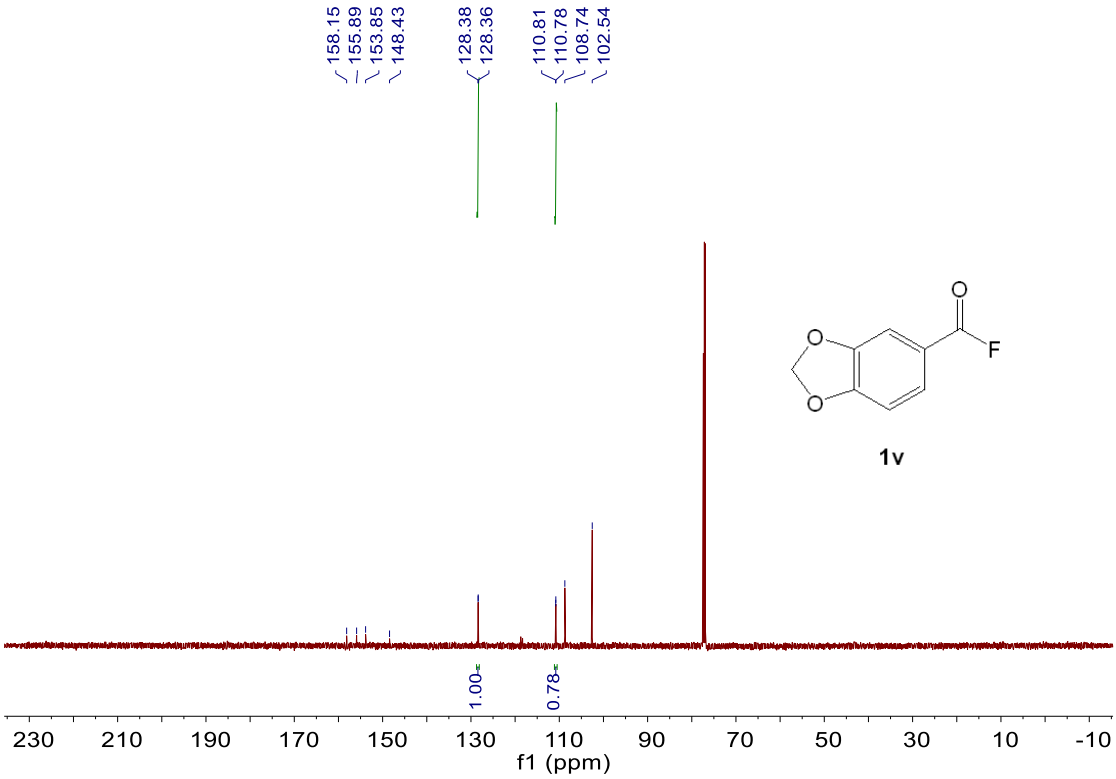


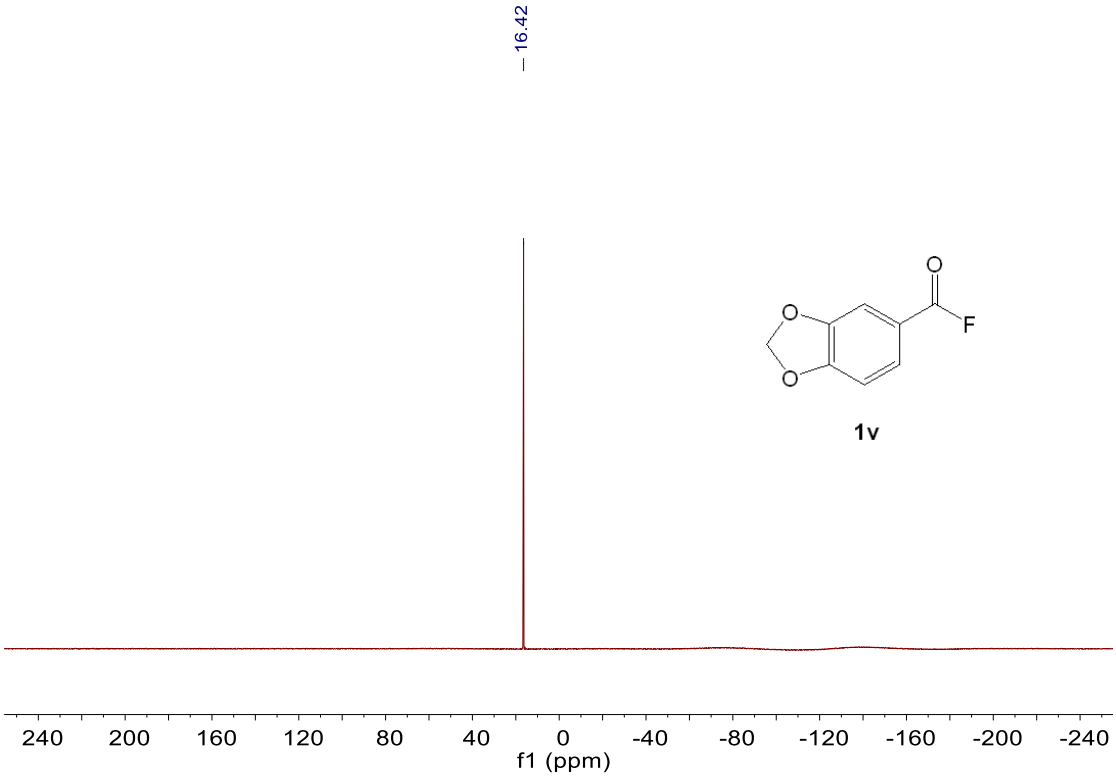
^{1}H NMR (400 MHz) spectrum of **1t** ($CDCl_3$, rt).



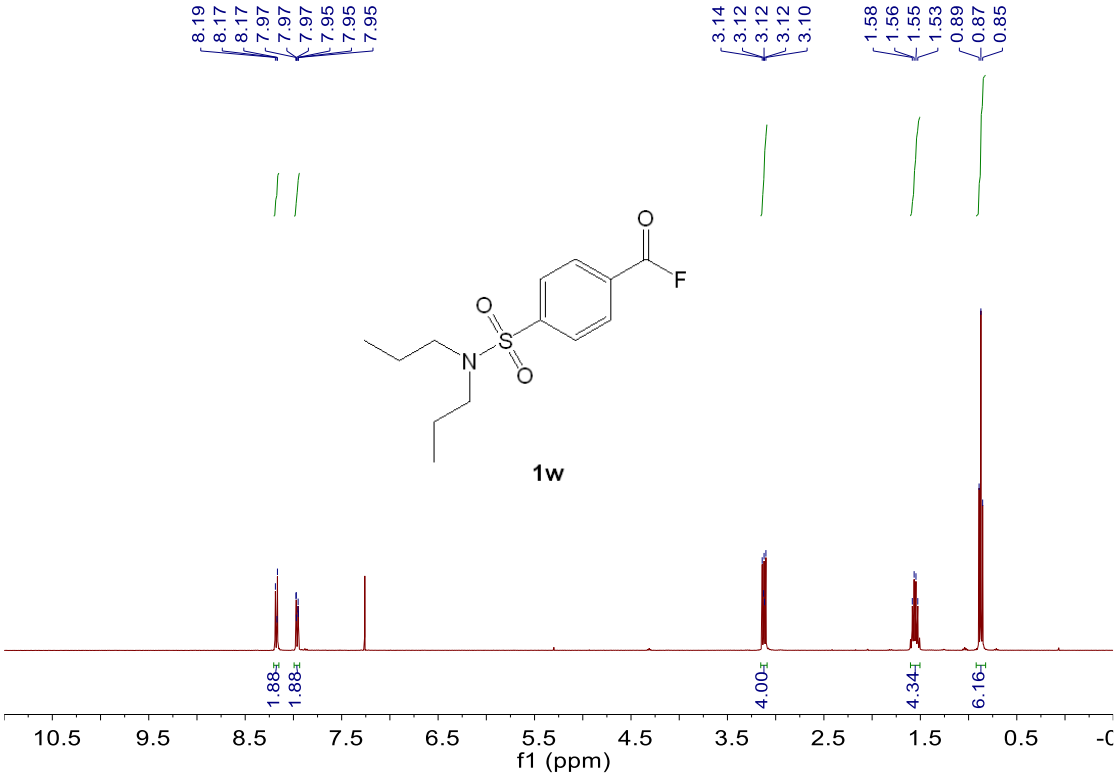
^{1}H NMR (400 MHz) spectrum of **1u** ($CDCl_3$, rt).

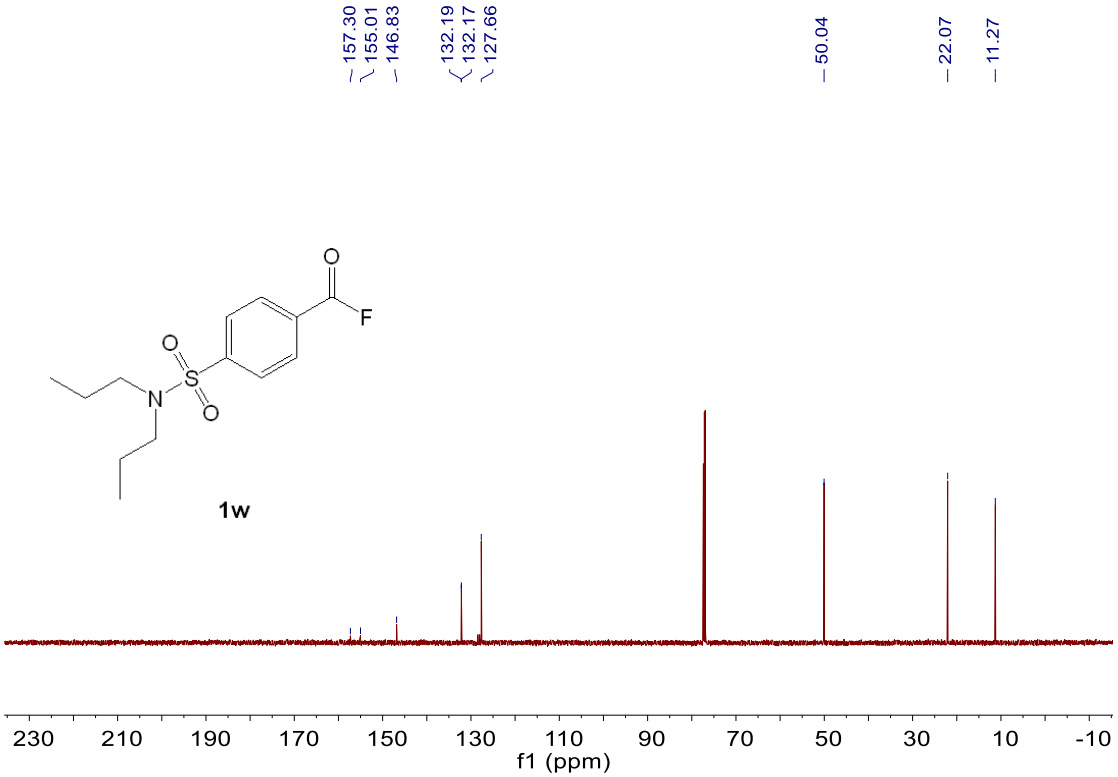

7.69
7.69
7.68
7.68
7.67
7.67
7.66
7.66
7.42
7.42
7.42
6.92
6.92
6.92
6.90
6.90
6.89
6.11
O
O
O
F
1v
1.00
0.96
1.00
2.06
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

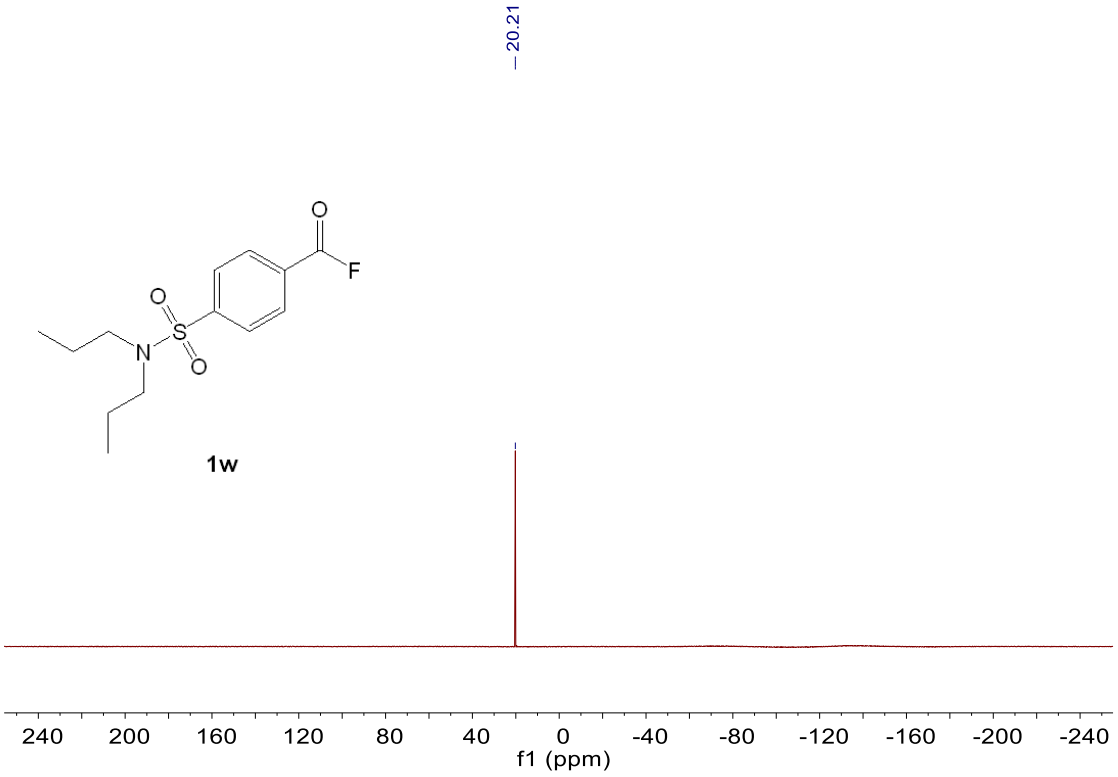

158.15
155.89
153.85
148.43
128.38
128.36
110.81
110.78
108.74
102.54
O
O
O
F
1v
1.00
0.78
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)



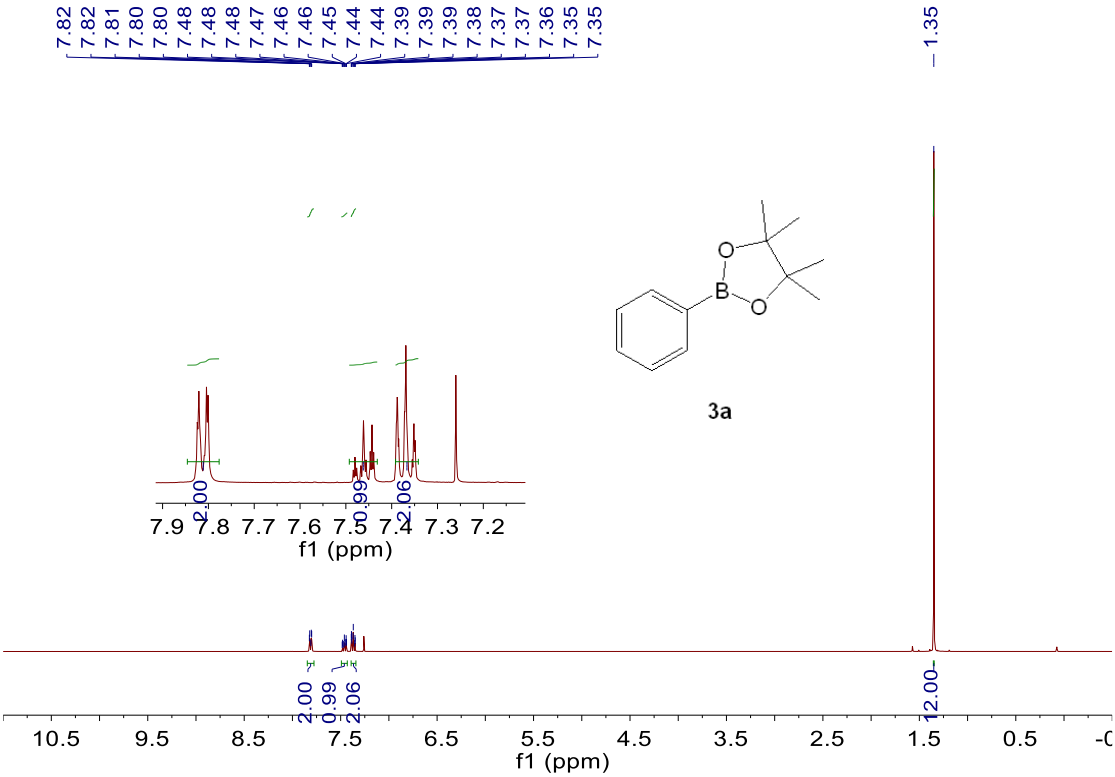
^{1}H NMR (400 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{19}F{^{1}H} NMR (376 MHz) spectra of **1v** ($CDCl_3$, rt).

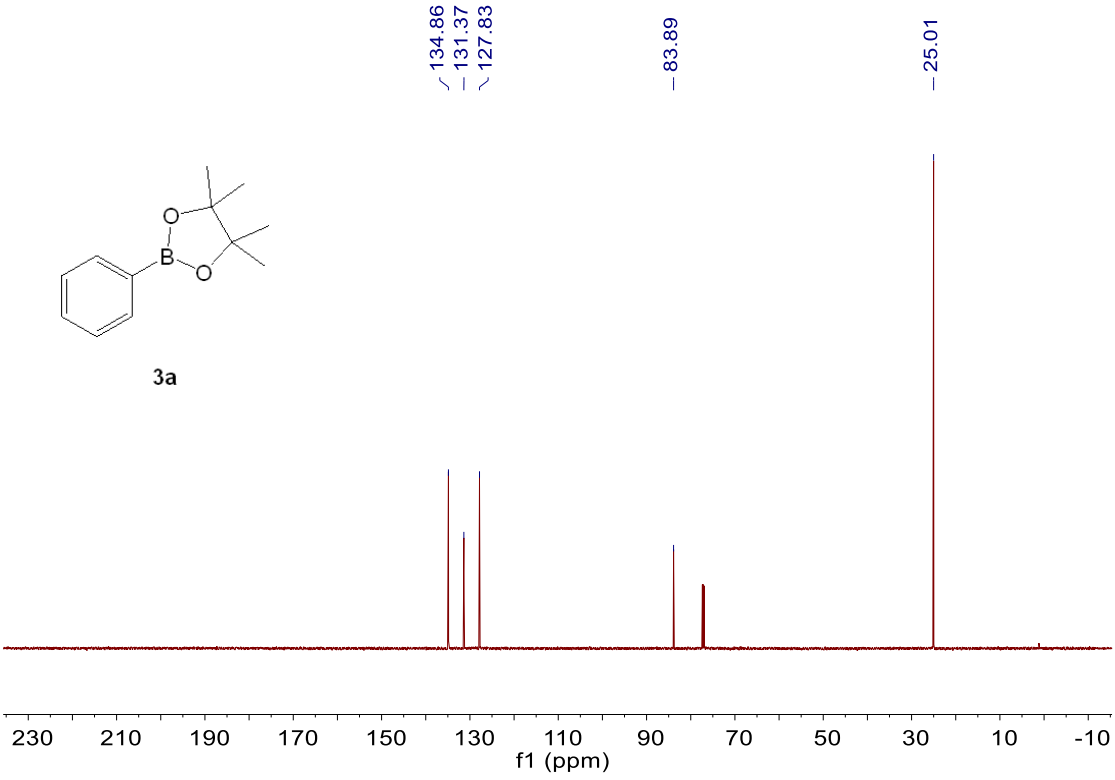


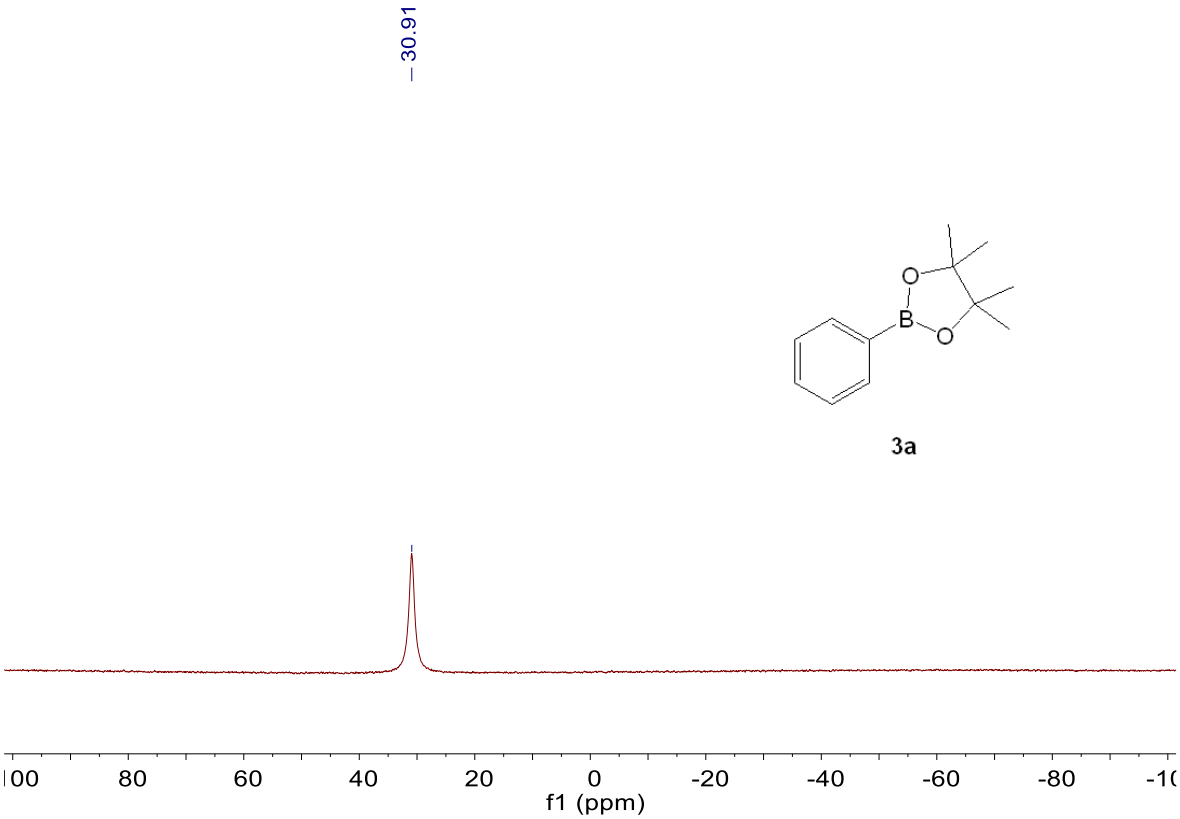




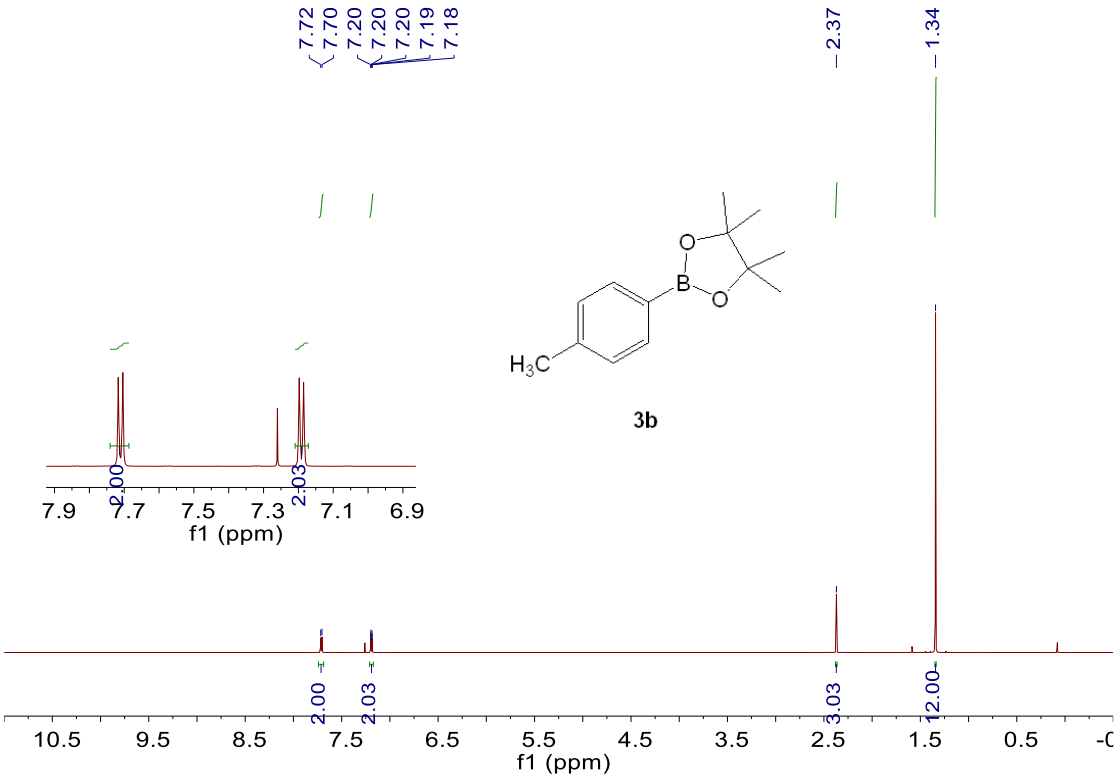
^{1}H NMR (400 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{19}F{^{1}H} NMR (376 MHz) spectra of **1w** ($CDCl_3$, rt).

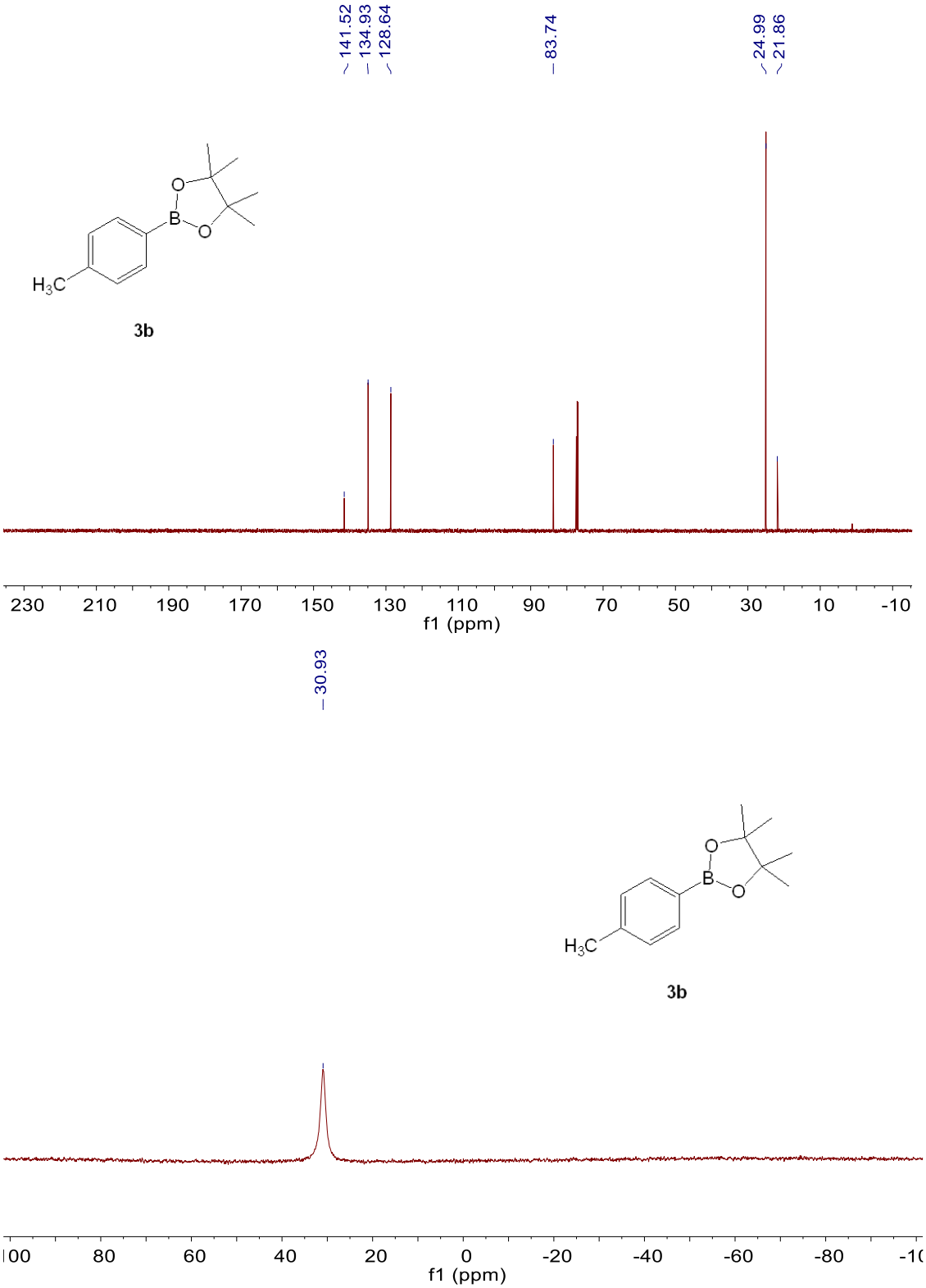

7.82
7.82
7.81
7.80
7.80
7.48
7.48
7.48
7.47
7.46
7.46
7.45
7.44
7.44
7.39
7.39
7.39
7.38
7.37
7.37
7.36
7.35
7.35
1.35
3a
2.00
0.99
2.06
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2
f1 (ppm)
2.00
0.99
2.06
12.00
10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)


134.86
131.37
127.83
83.89
25.01
3a
230 210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)

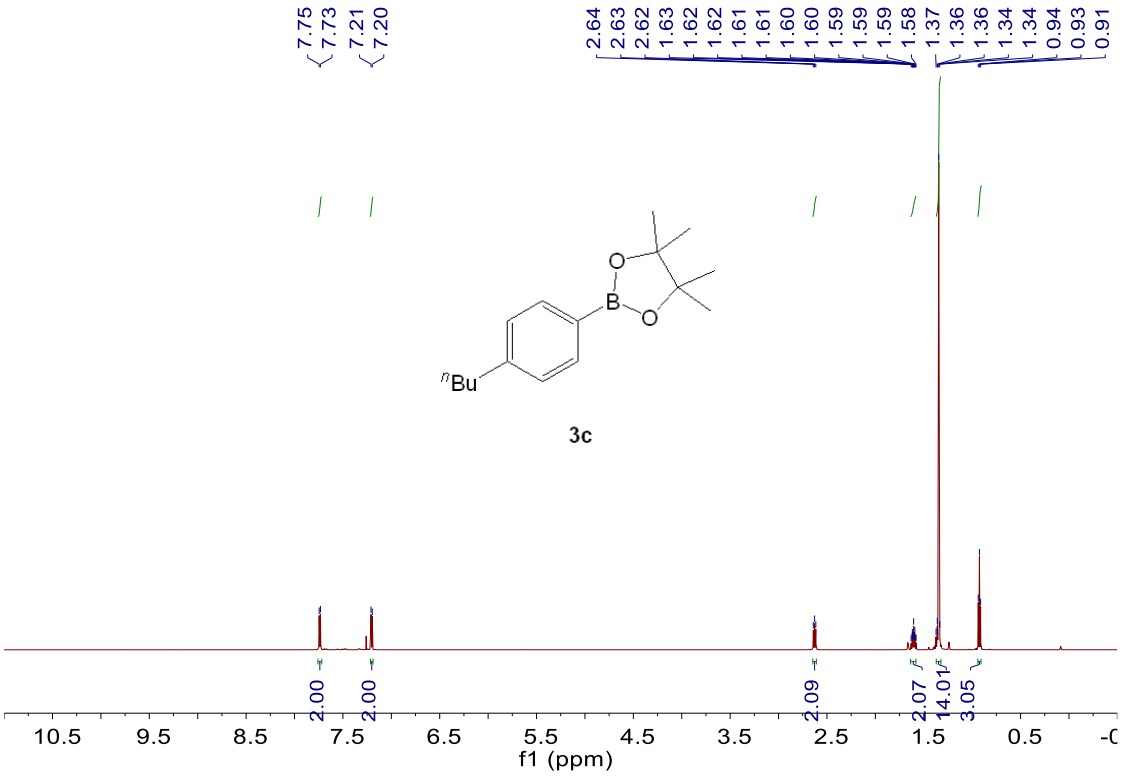


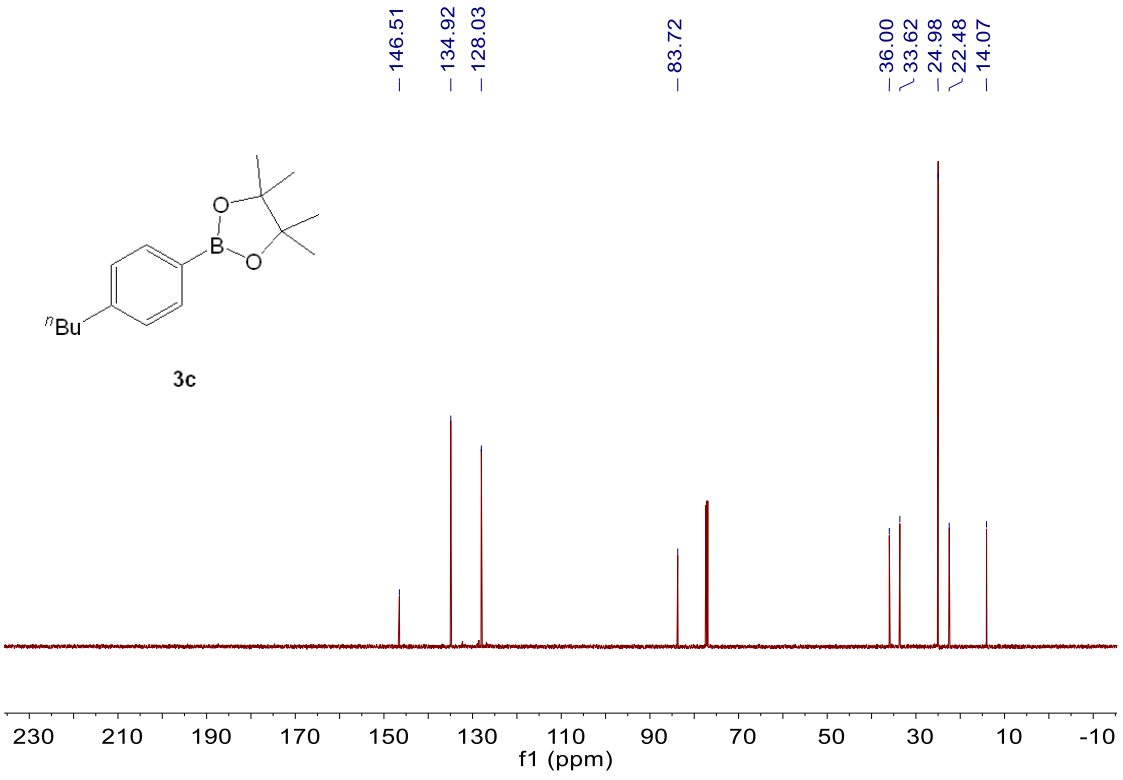
^{1}H NMR (400 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3a** ($CDCl_3$, rt).

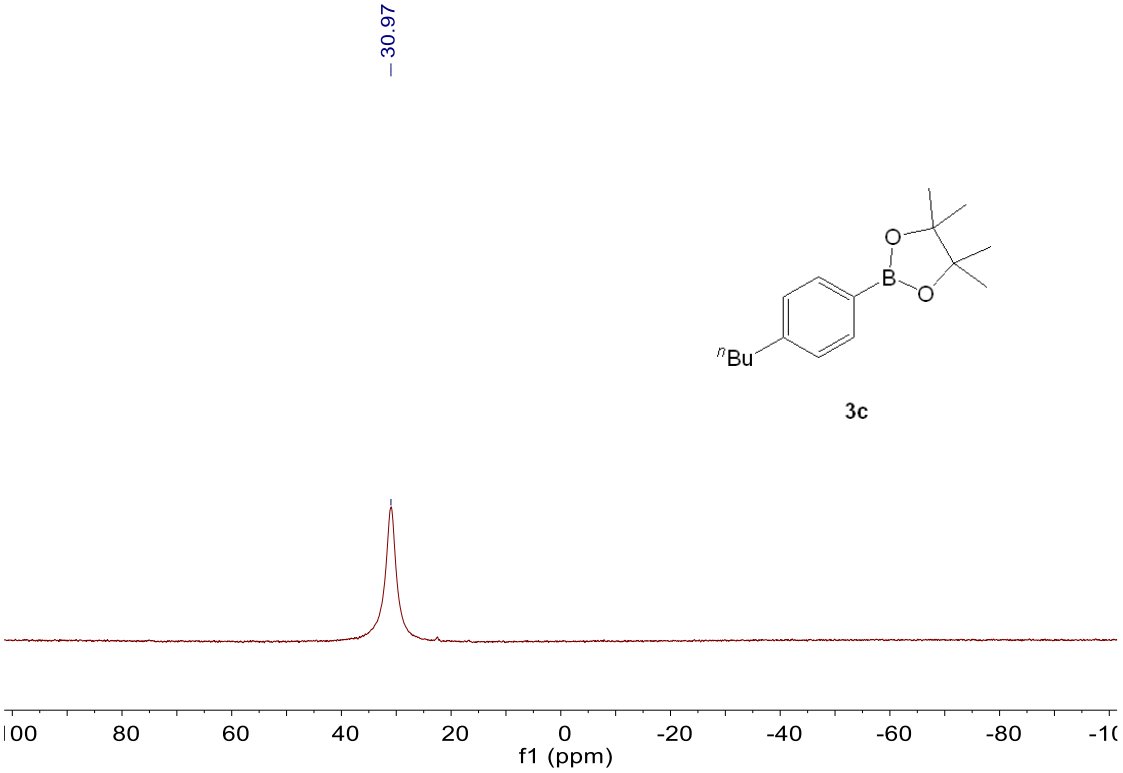




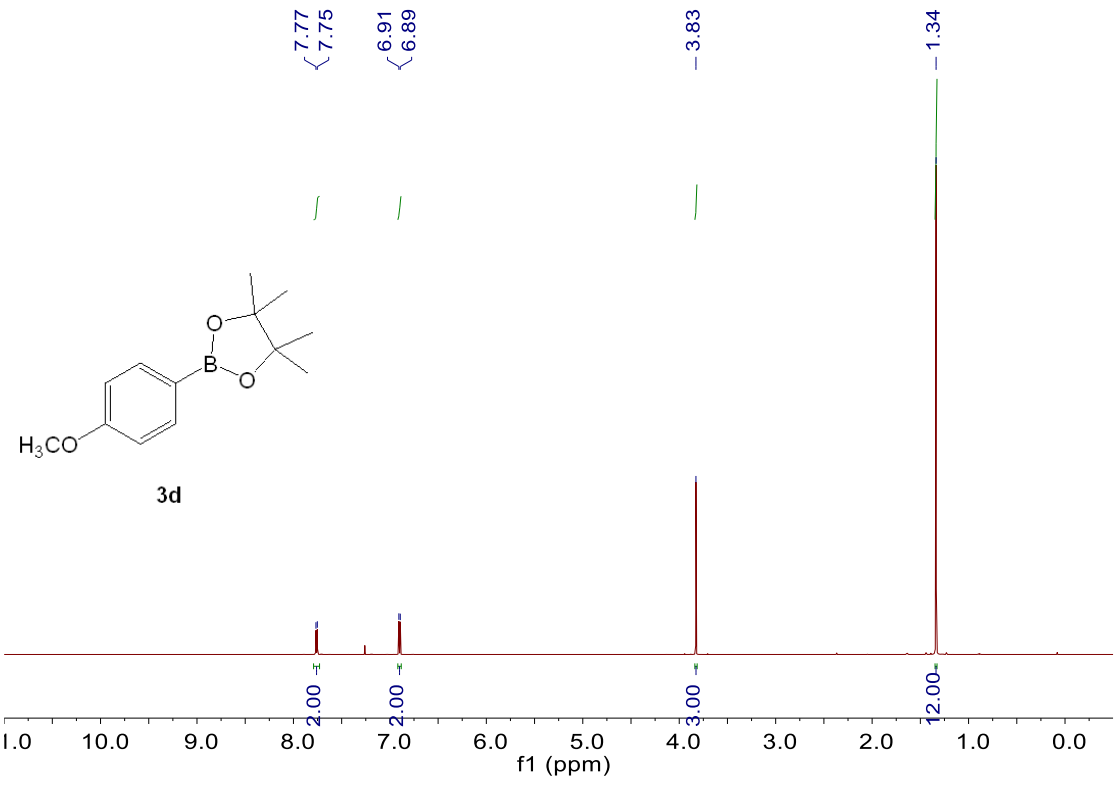
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3b** ($CDCl_3$, rt).

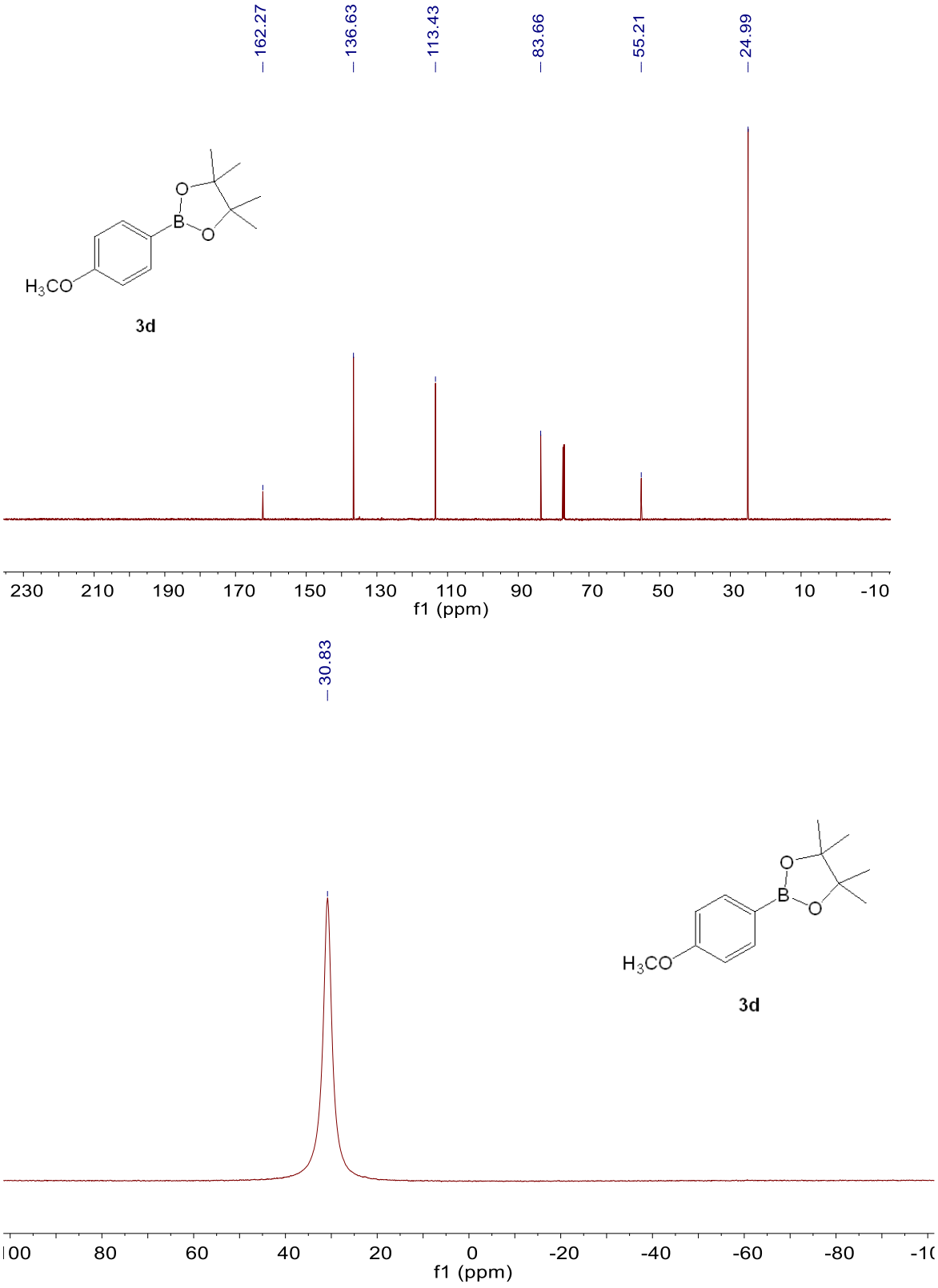

7.75
7.73
7.21
7.20
2.64
2.63
2.62
1.63
1.62
1.62
1.61
1.61
1.60
1.60
1.59
1.59
1.59
1.58
1.37
1.36
1.36
1.34
1.34
0.94
0.93
0.91
O
B
O
nBu
3c
2.00
2.00
2.09
2.07
14.01
3.05
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


146.51
134.92
128.03
83.72
36.00
33.62
24.98
22.48
14.07
O
B
O
nBu
3c
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

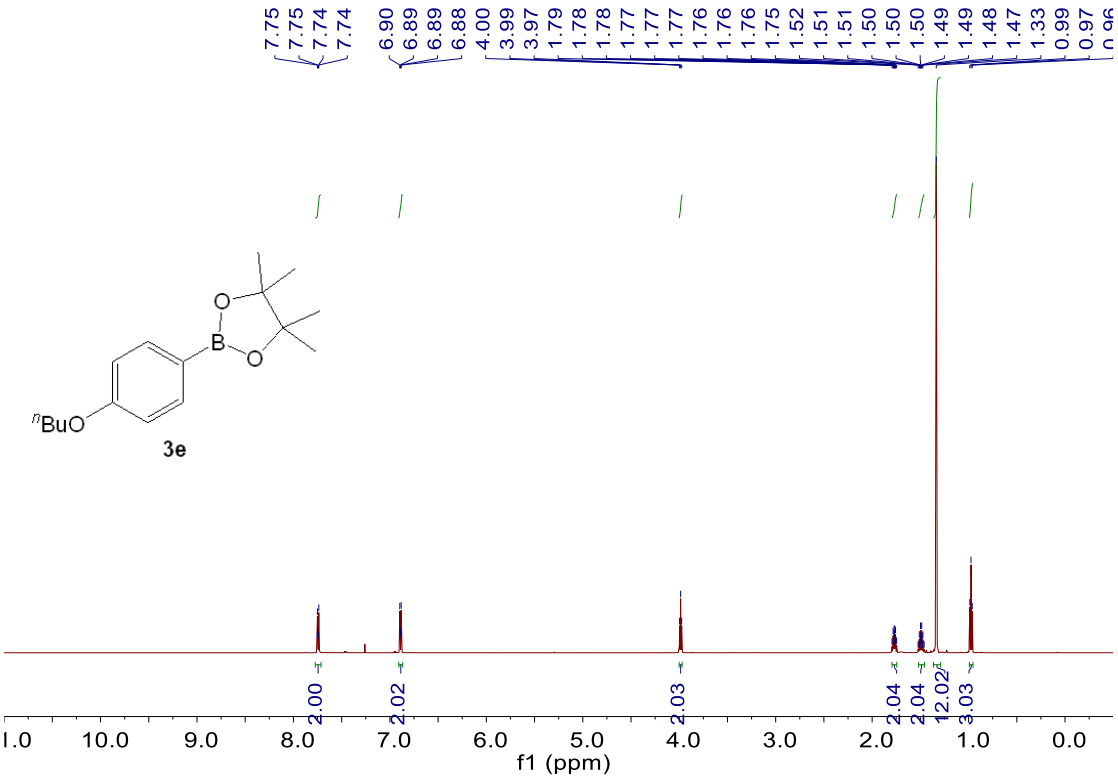


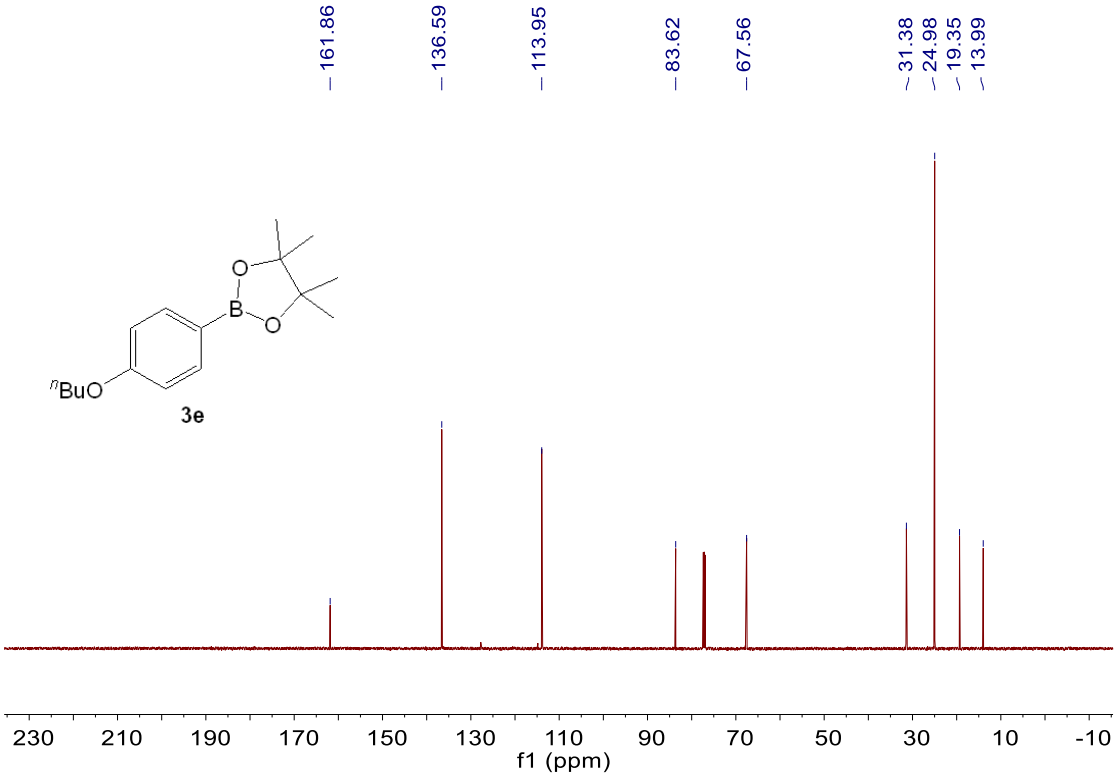
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3c** ($CDCl_3$, rt).

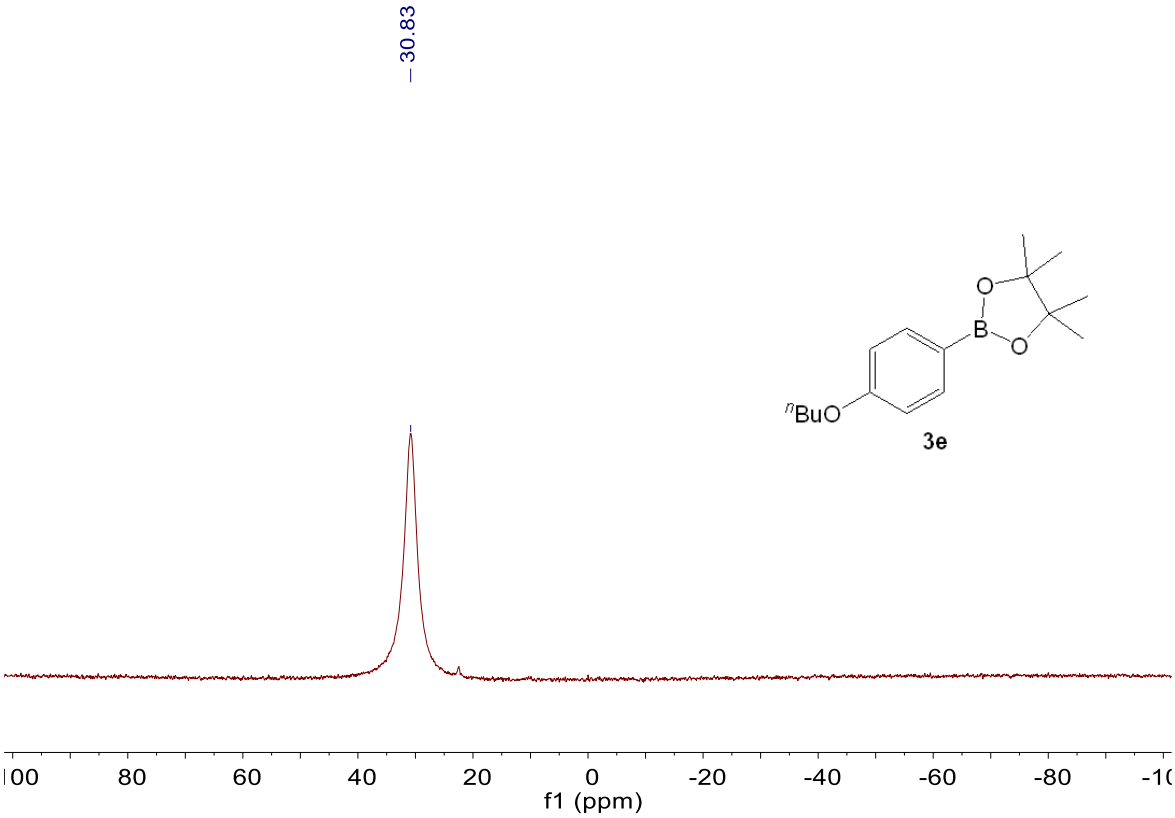




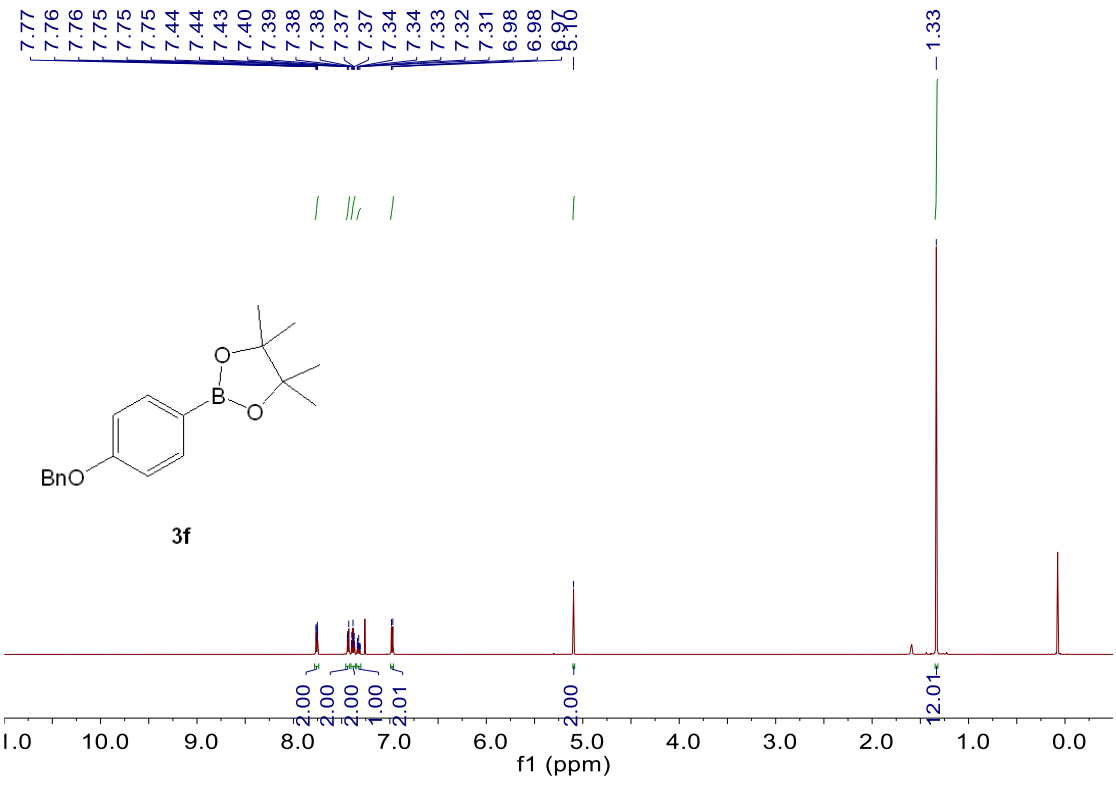
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3d** ($CDCl_3$, rt).

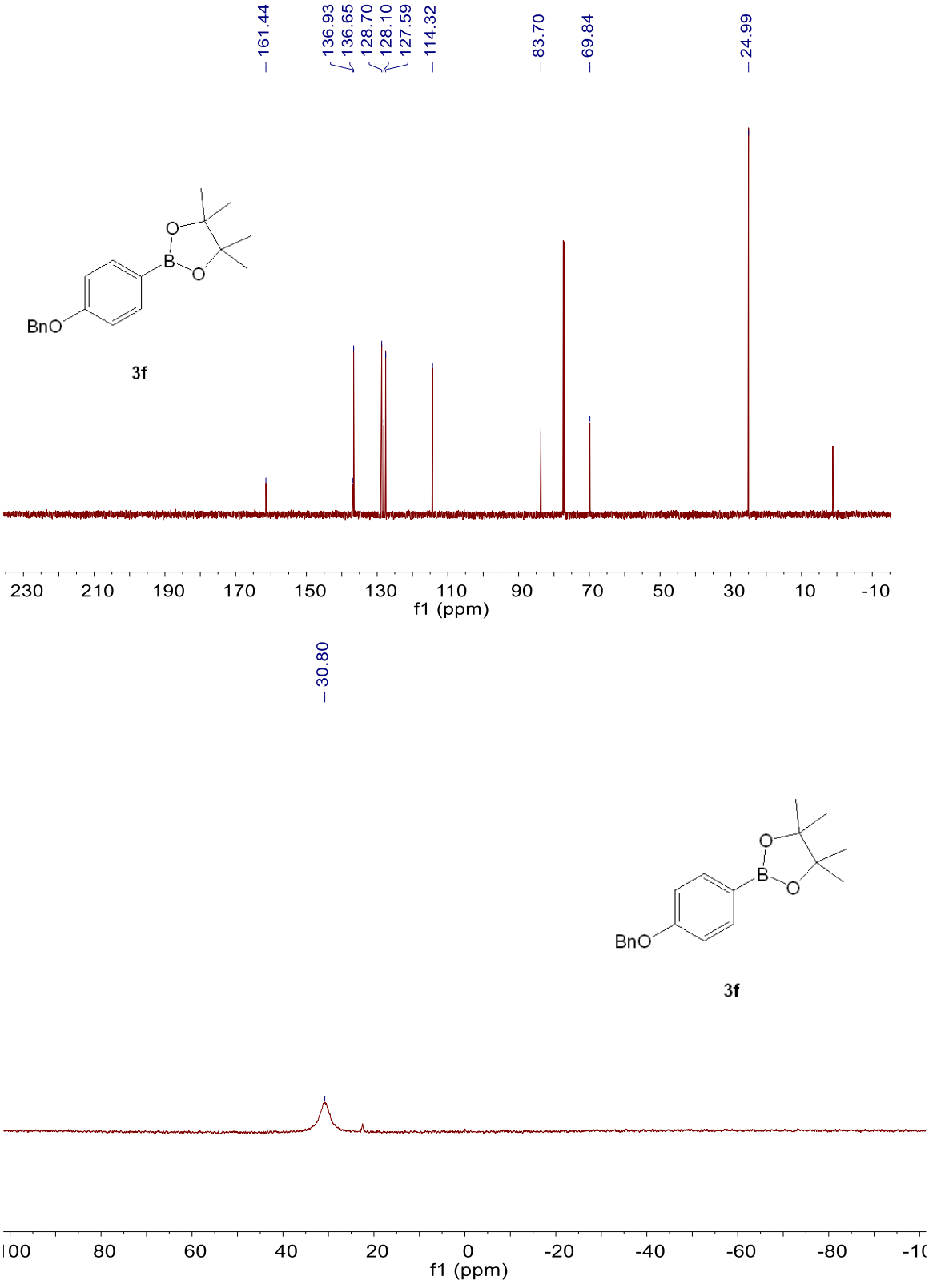

7.75
7.75
7.74
7.74
6.90
6.89
6.89
6.88
4.00
3.99
3.97
1.79
1.78
1.78
1.77
1.77
1.77
1.76
1.76
1.76
1.75
1.52
1.51
1.51
1.50
1.50
1.50
1.49
1.49
1.48
1.47
1.33
0.99
0.97
O
B
O
nBuO
3e
2.00
2.02
2.03
2.04
2.04
12.02
3.03
f1 (ppm)


161.86
136.59
113.95
83.62
67.56
31.38
24.98
19.35
13.99
O
B
O
nBuO
3e
f1 (ppm)

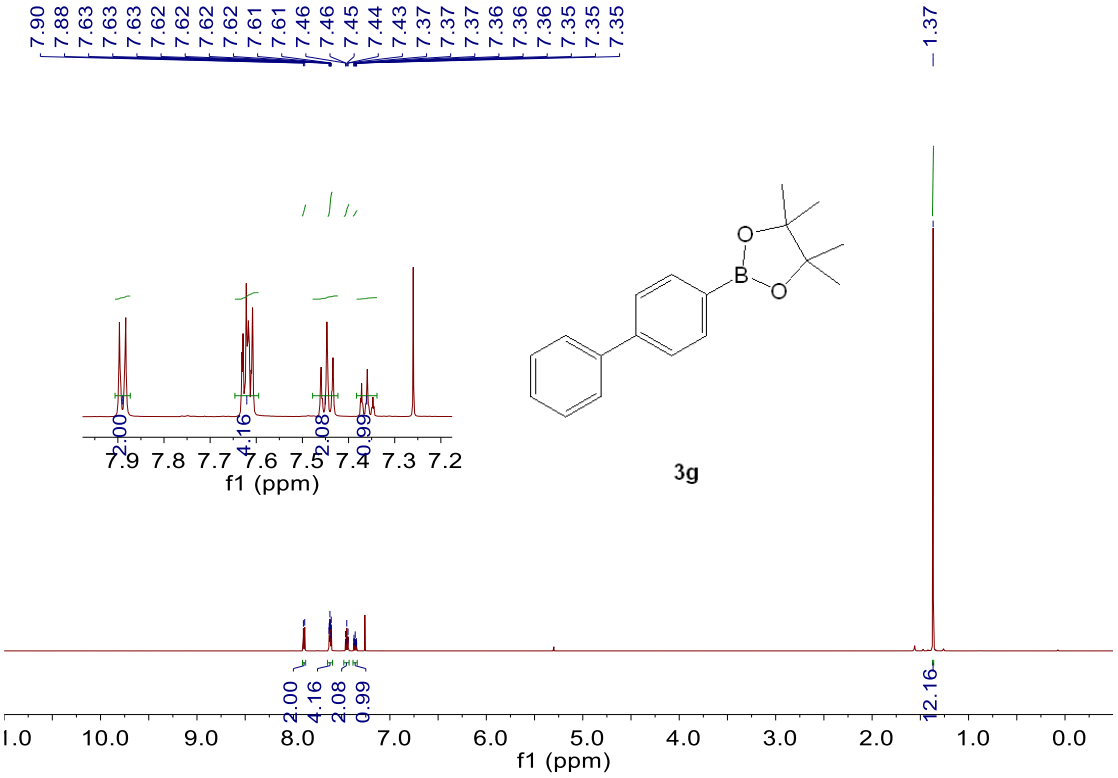


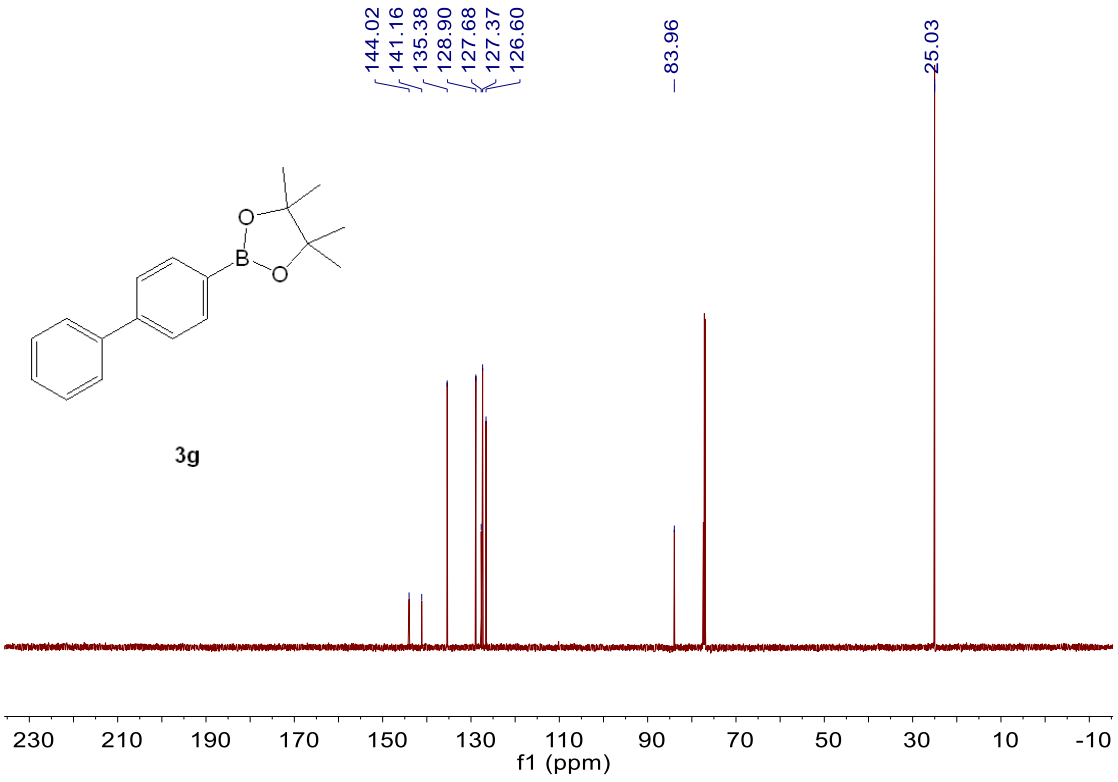
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3e** ($CDCl_3$, rt).

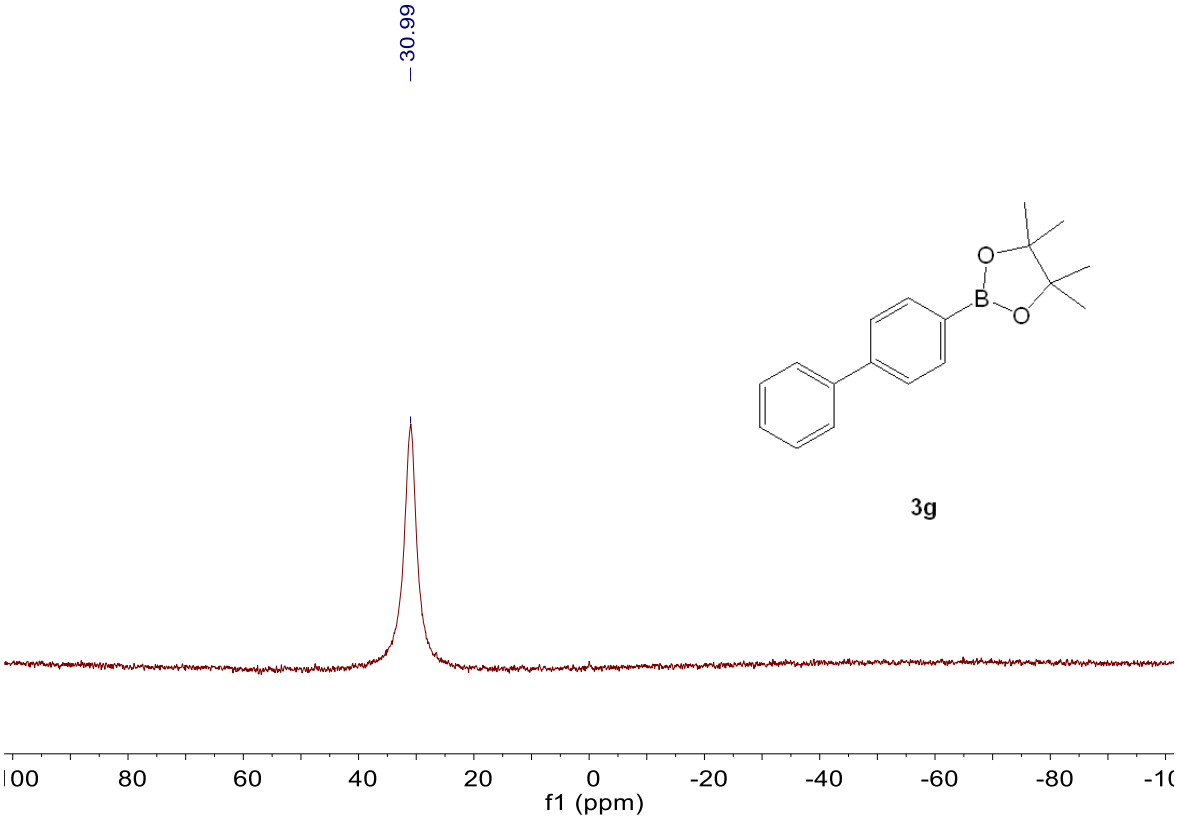




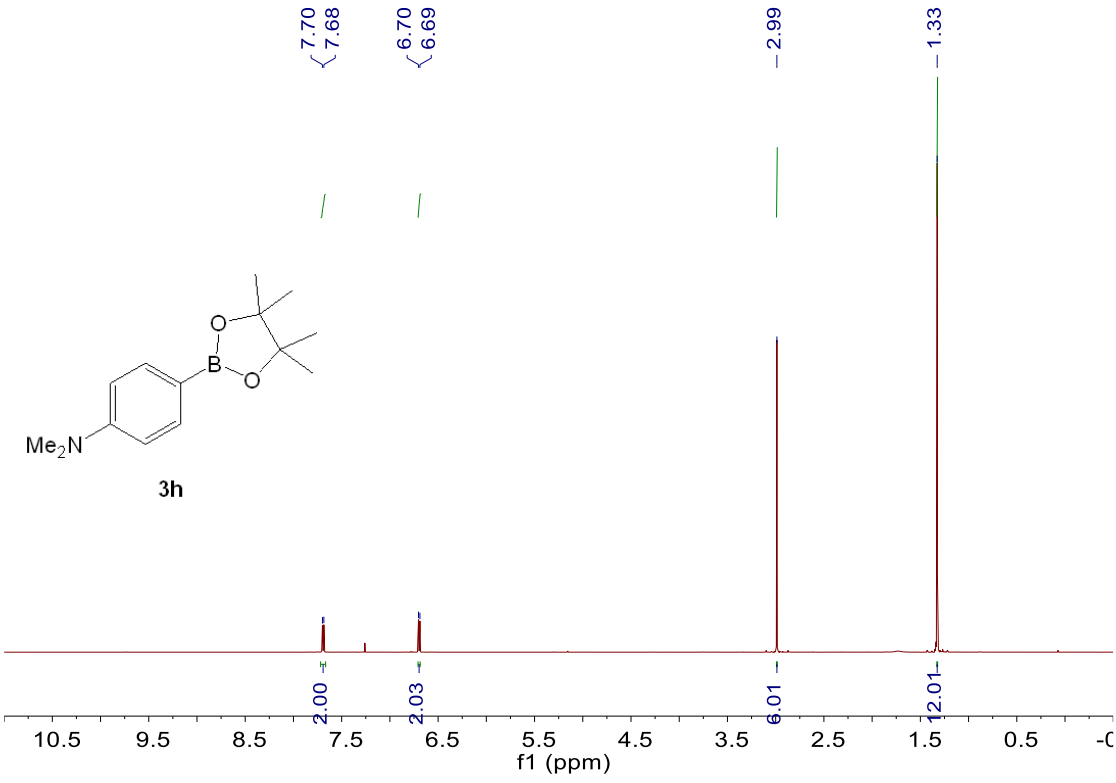
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3f** ($CDCl_3$, rt).

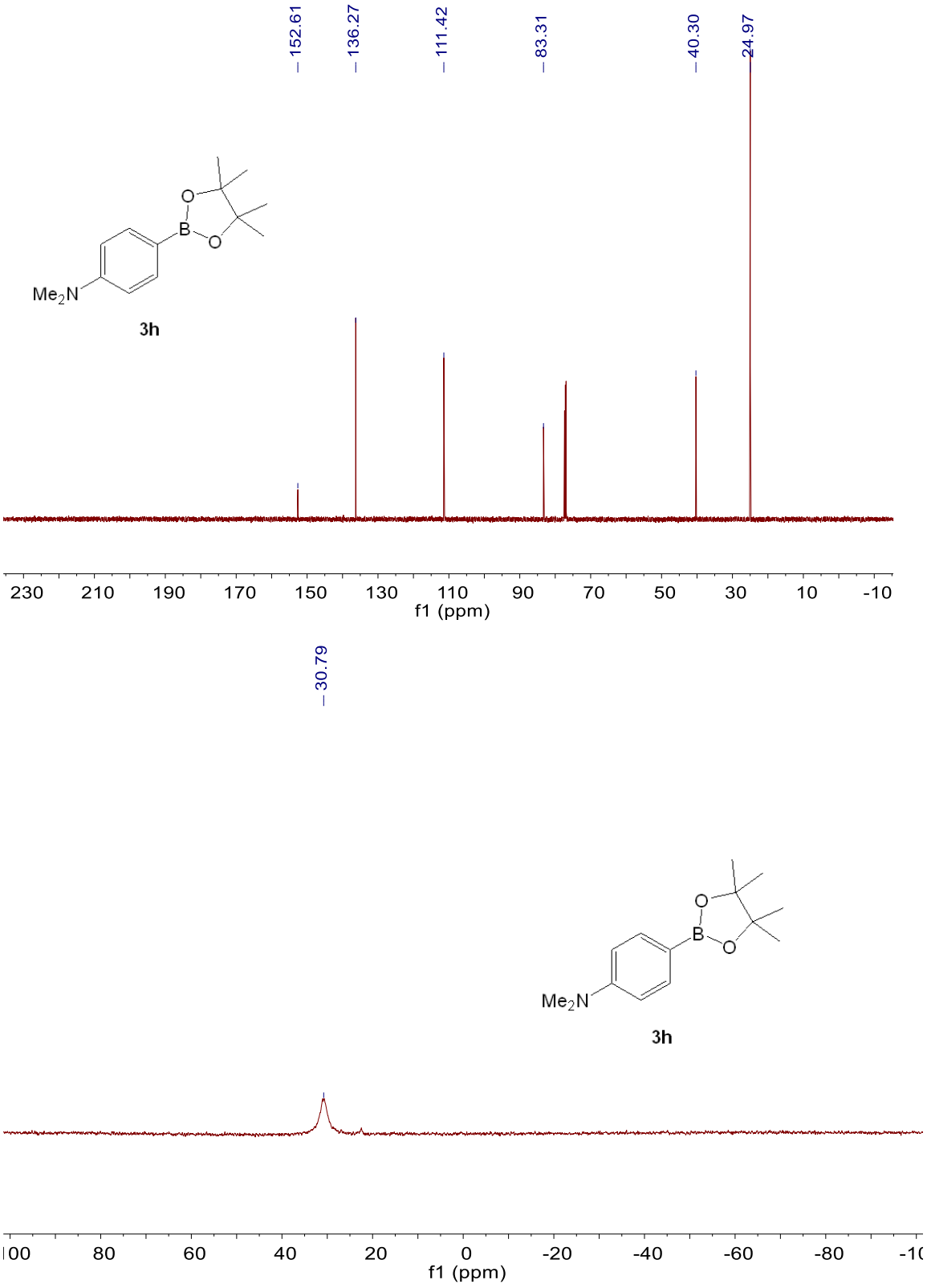

7.90
7.88
7.63
7.63
7.63
7.62
7.62
7.62
7.62
7.61
7.61
7.46
7.45
7.44
7.43
7.37
7.37
7.37
7.36
7.36
7.36
7.35
7.35
7.35
1.37
2.00
4.16
2.08
0.99
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2
f1 (ppm)
O
B
O
3g
2.00
4.16
2.08
0.99
12.16
1.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)


144.02
141.16
135.38
128.90
127.68
127.37
126.60
83.96
25.03
O
B
O
3g
230 210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)

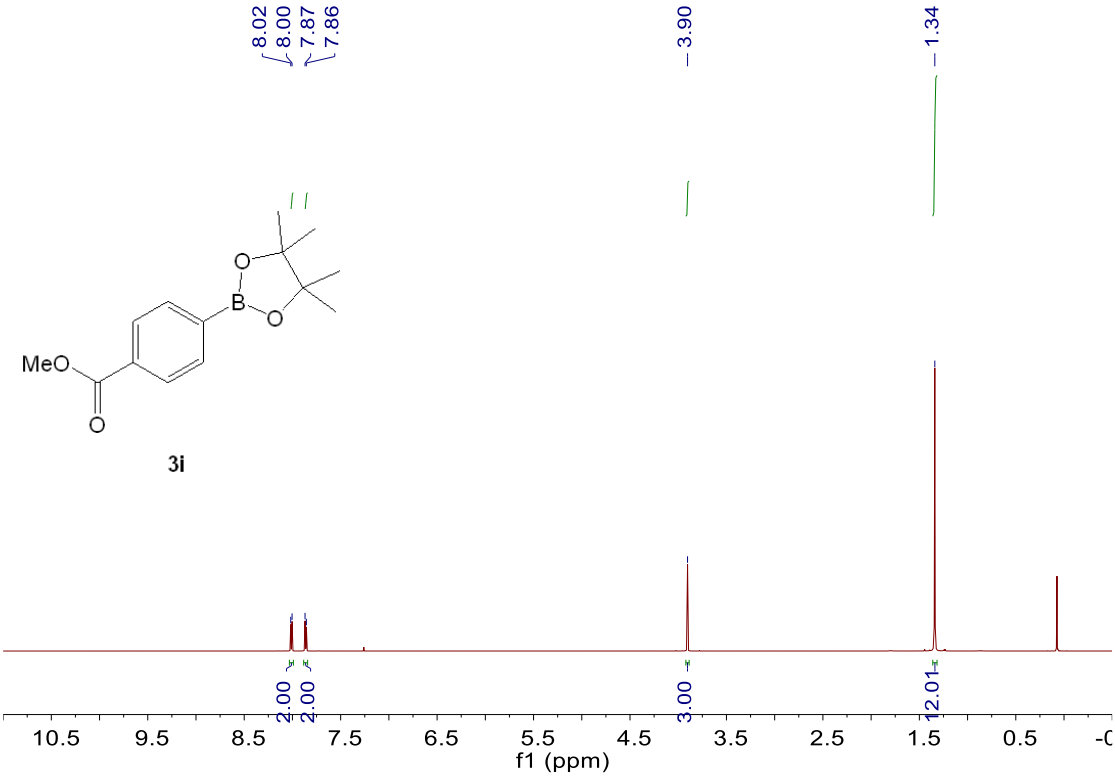


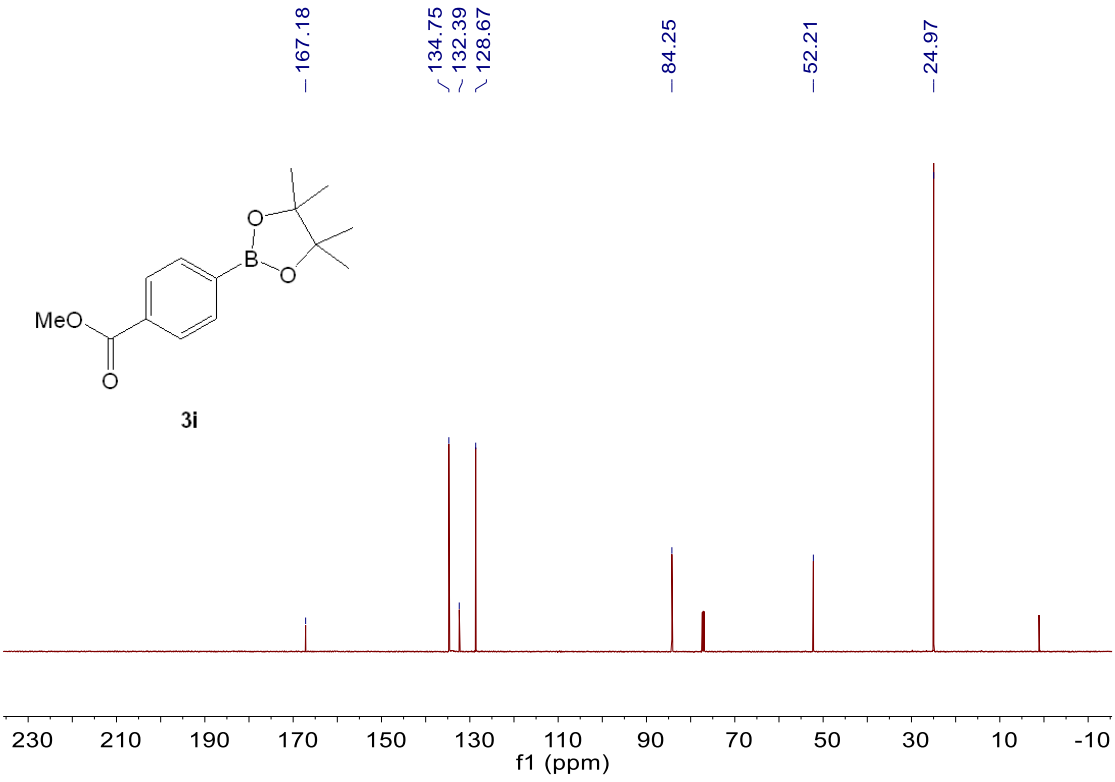
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3g** ($CDCl_3$, rt).

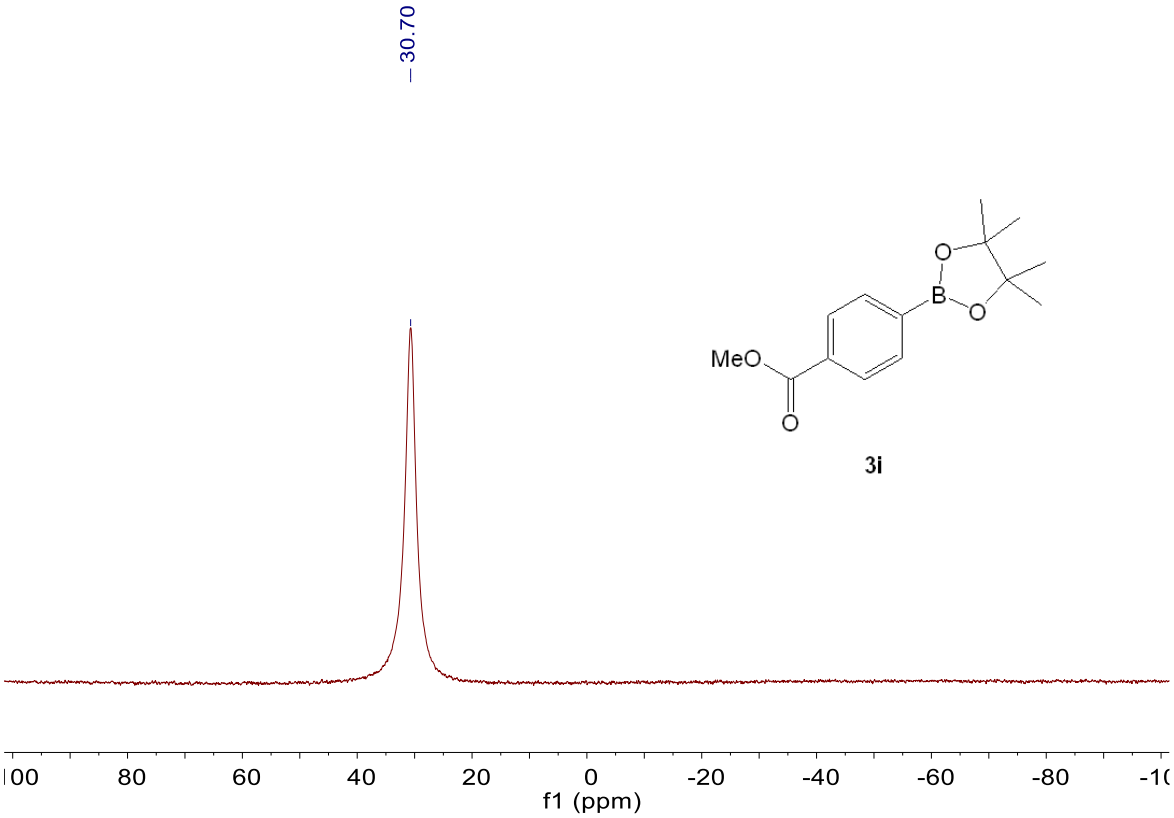




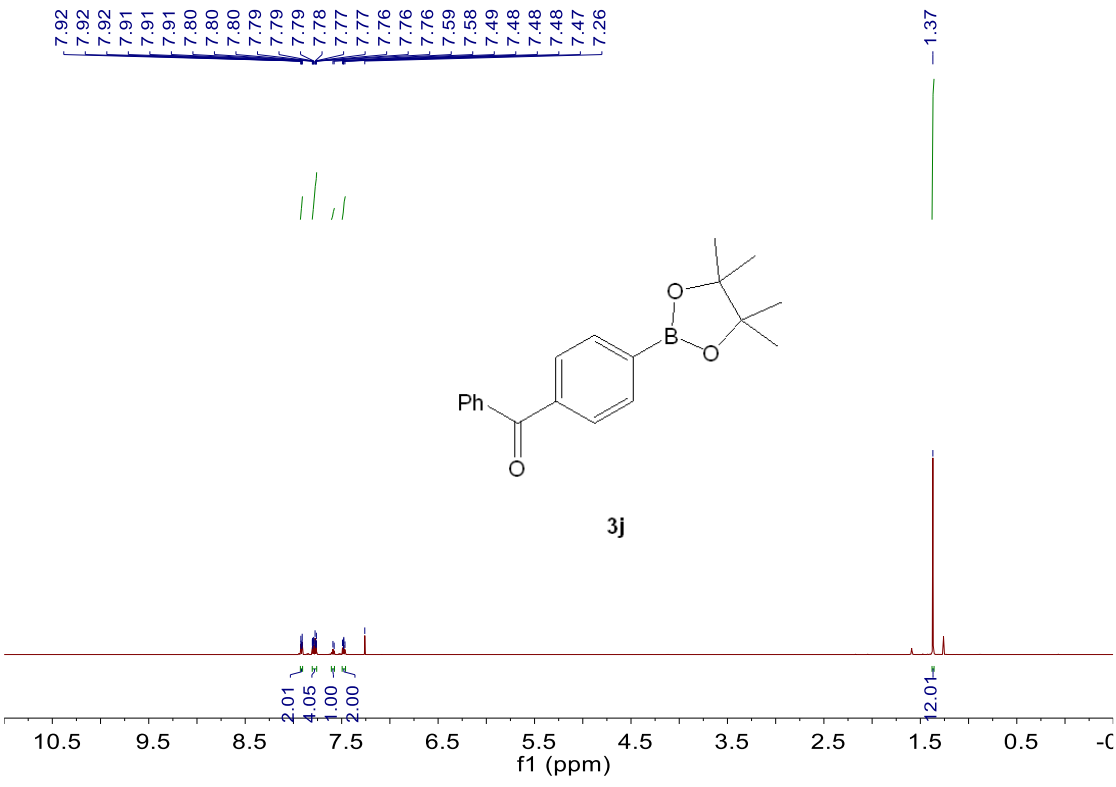
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3h** ($CDCl_3$, rt).

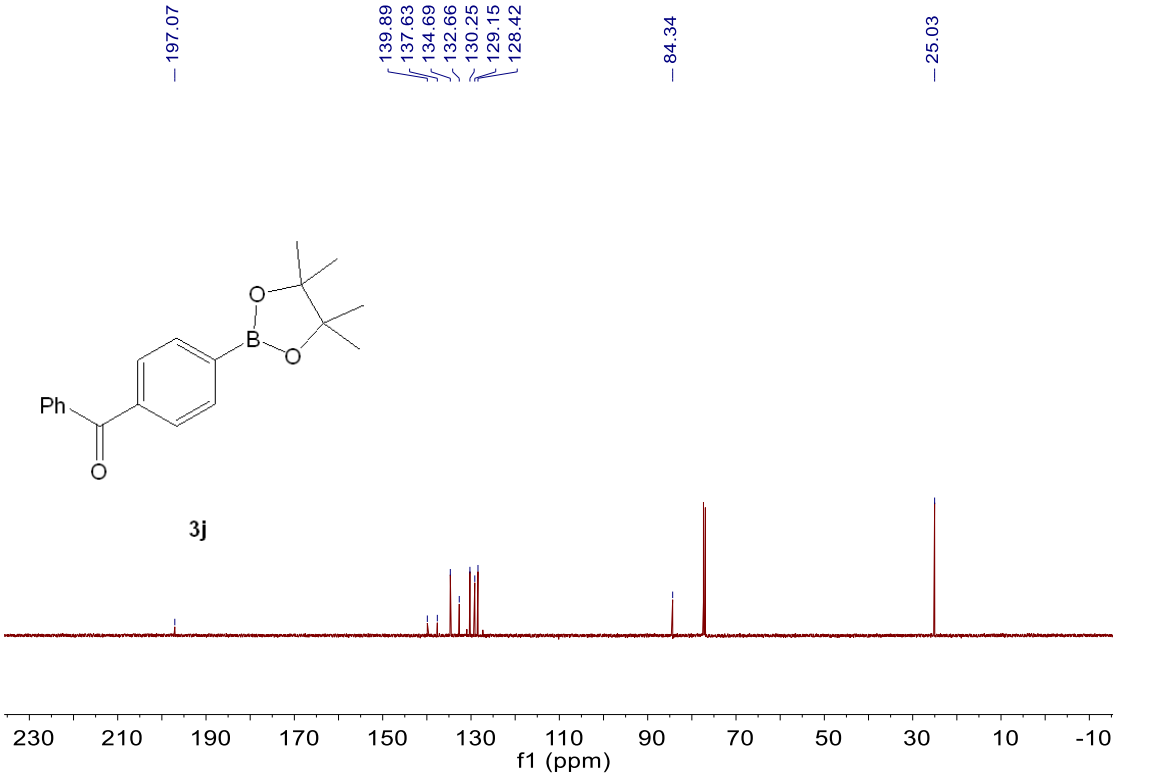

8.02
8.00
7.87
7.86
3.90
1.34
MeO
O
O
B
O
3i
2.00
2.00
3.00
12.01
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

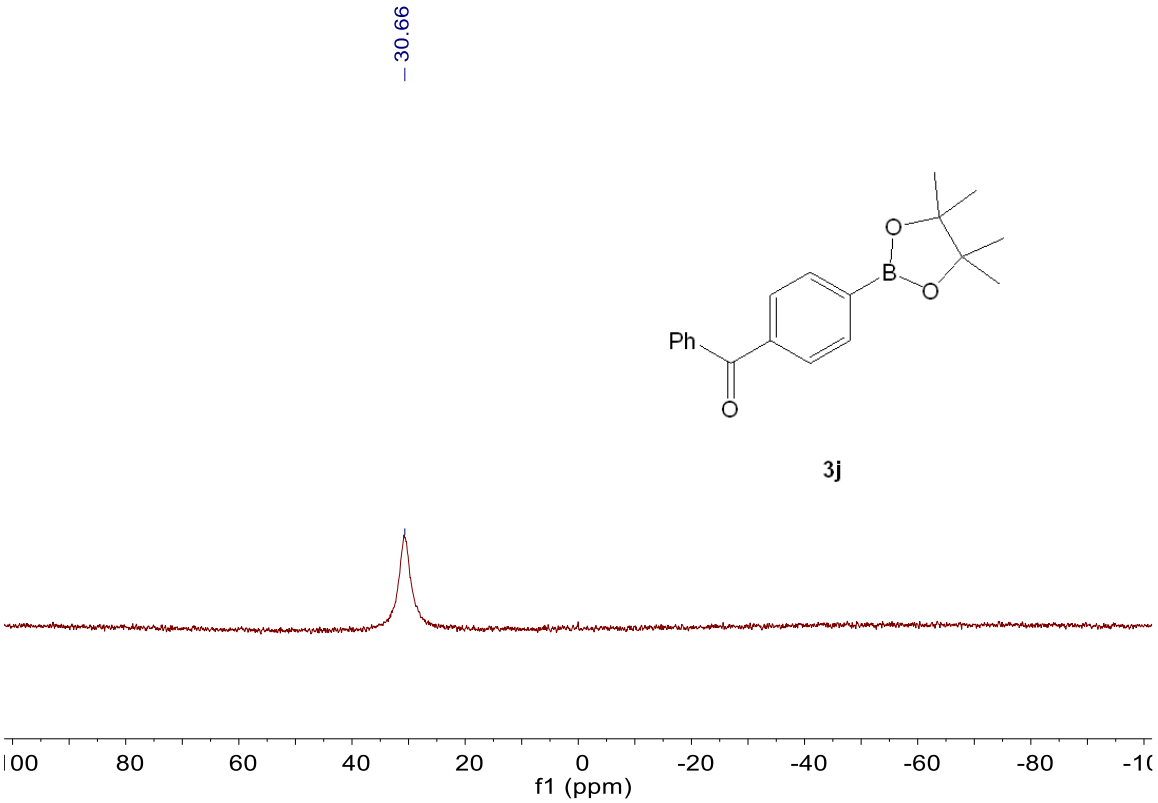

167.18
134.75
132.39
128.67
84.25
52.21
24.97
MeO
O
O
B
O
3i
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)



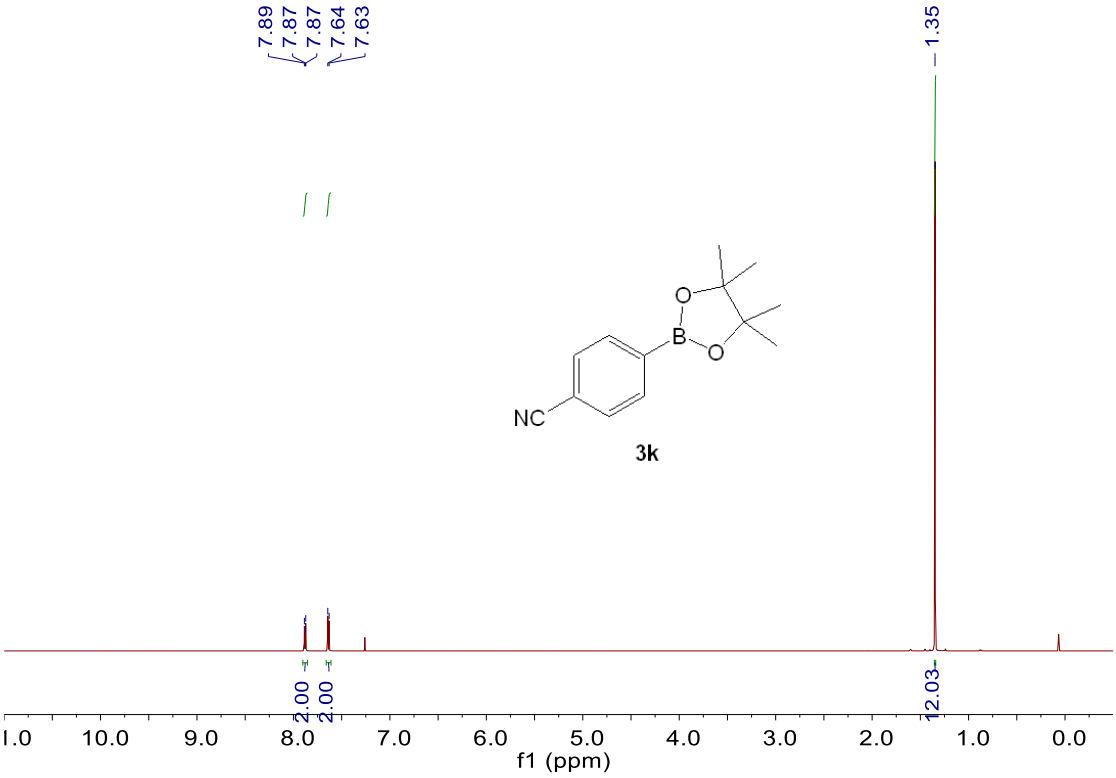
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3i** ($CDCl_3$, rt).

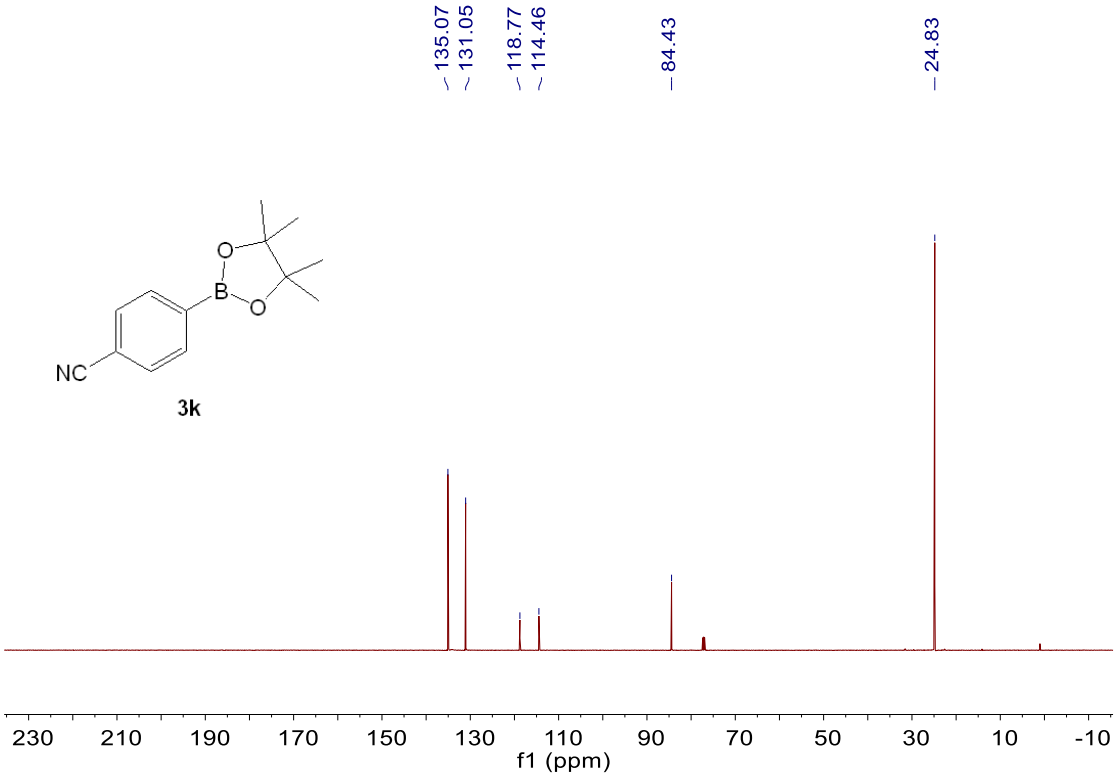


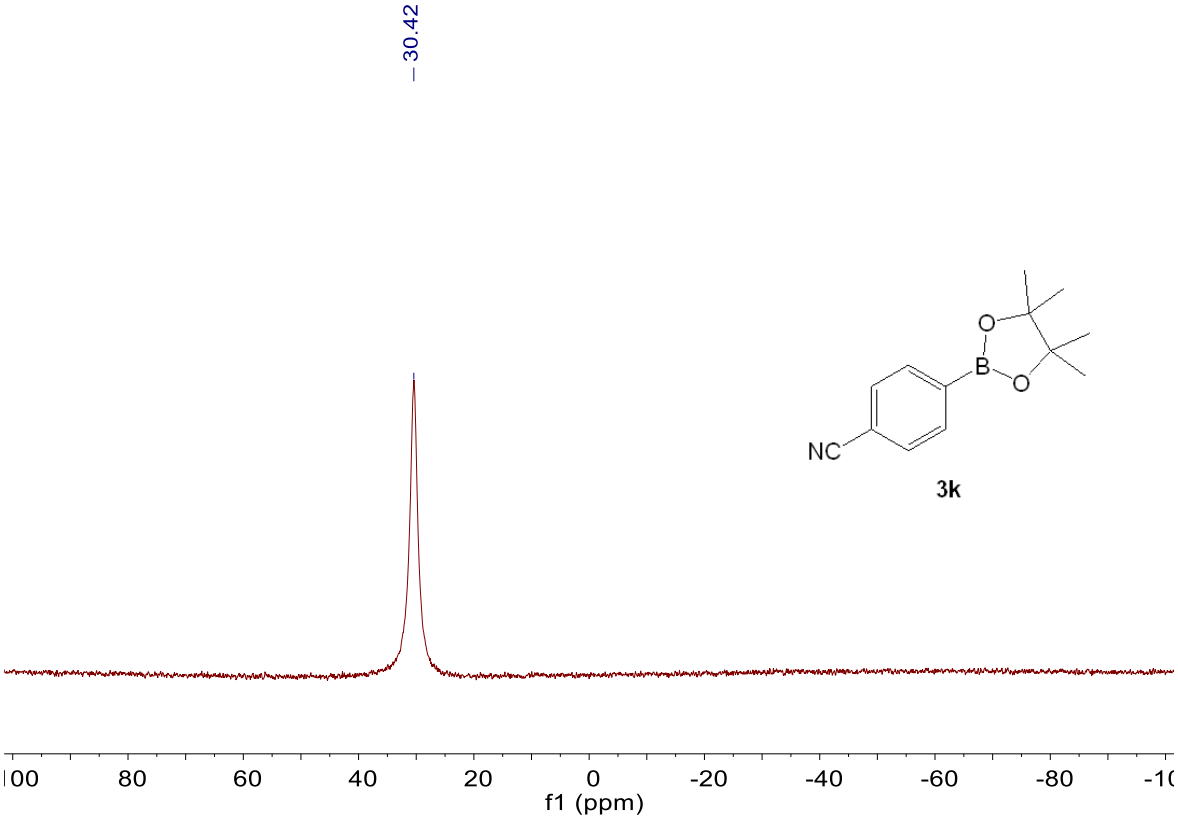




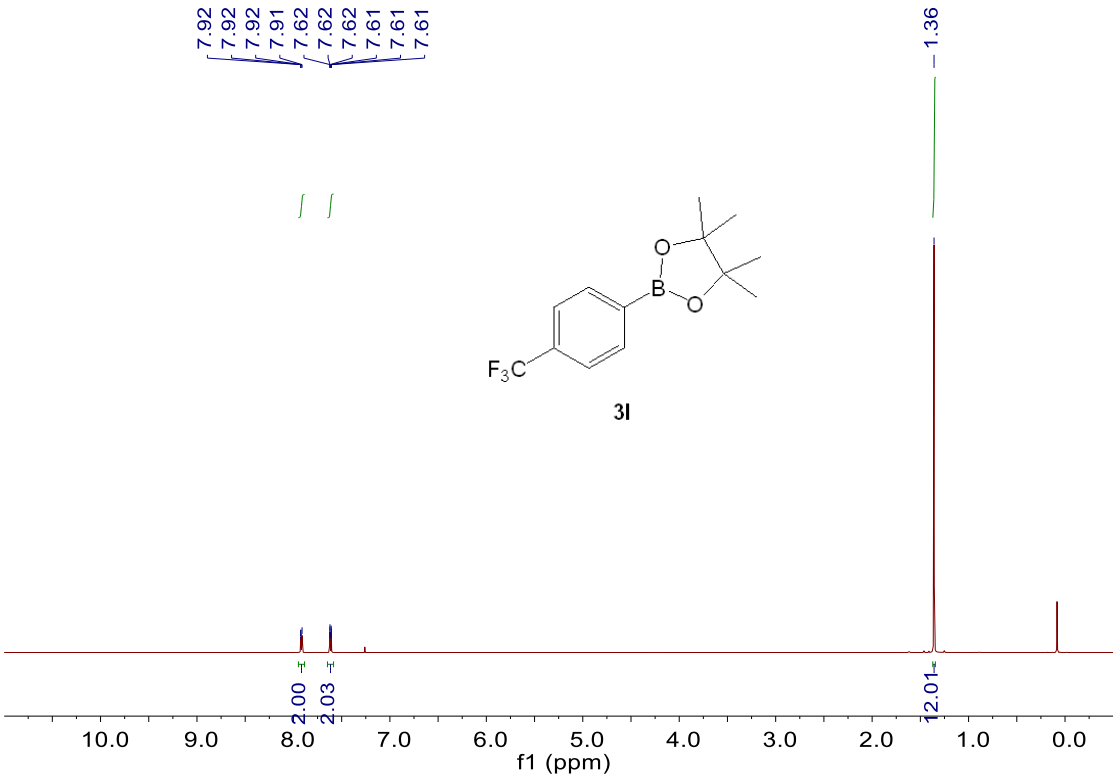
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3j** ($CDCl_3$, rt).

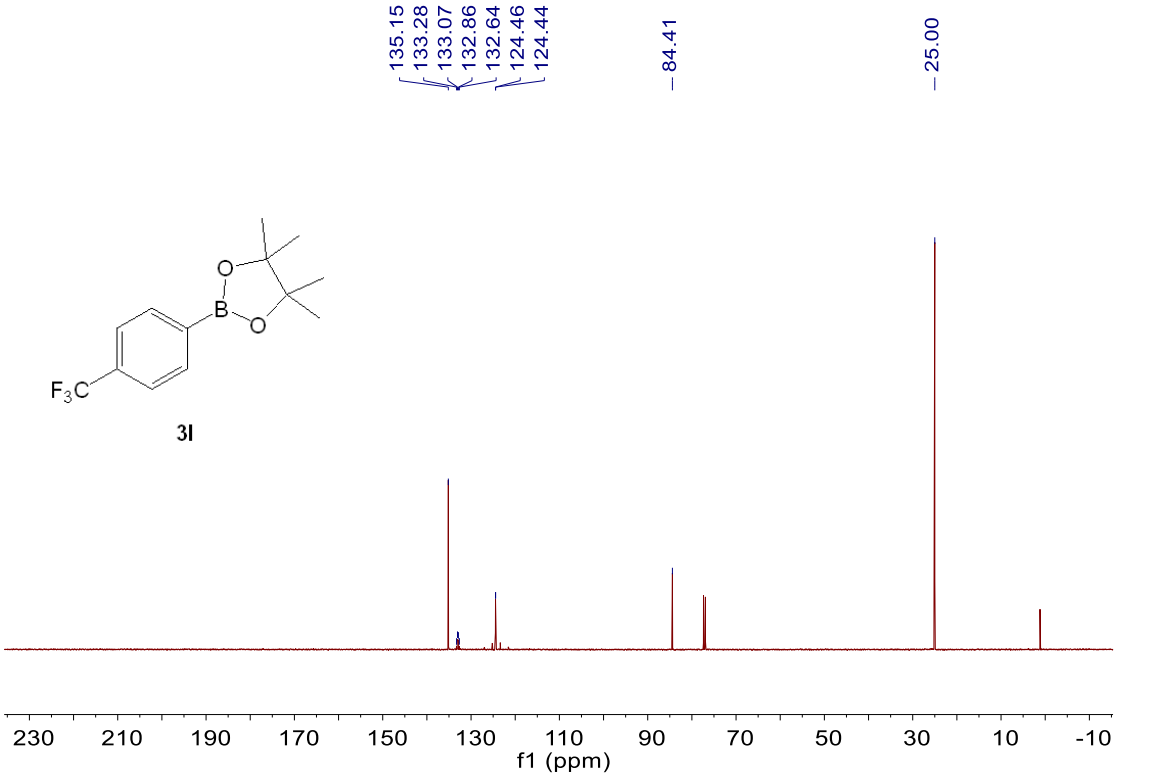

7.89
7.87
7.87
7.64
7.63
1.35
O
B
O
NC
3k
2.00
2.00
12.03
f1 (ppm)

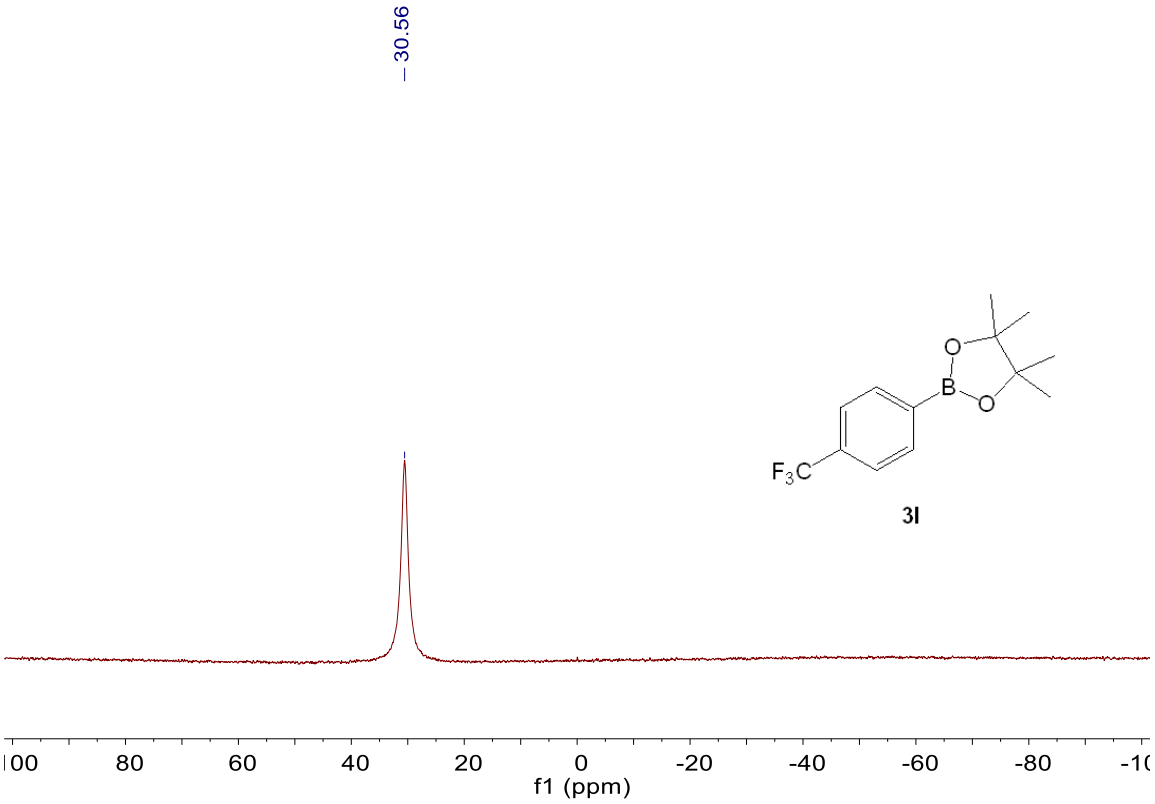

135.07
131.05
118.77
114.46
84.43
24.83
O
B
O
NC
3k
f1 (ppm)



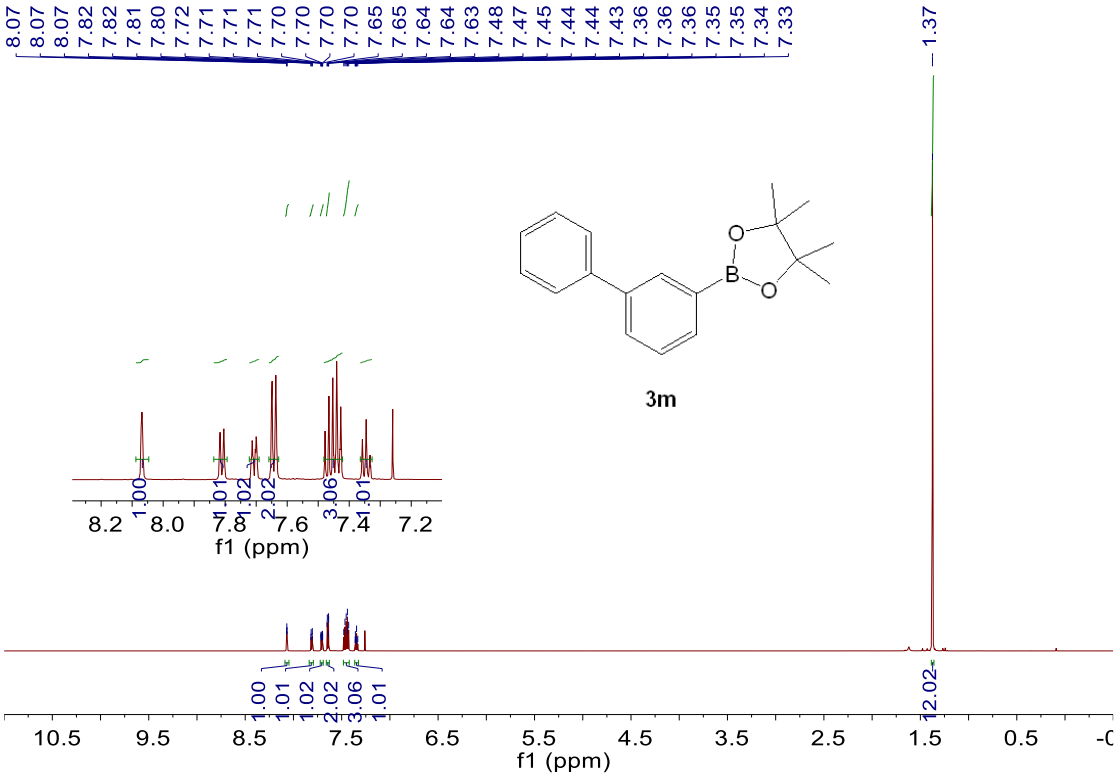
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3k** ($CDCl_3$, rt).

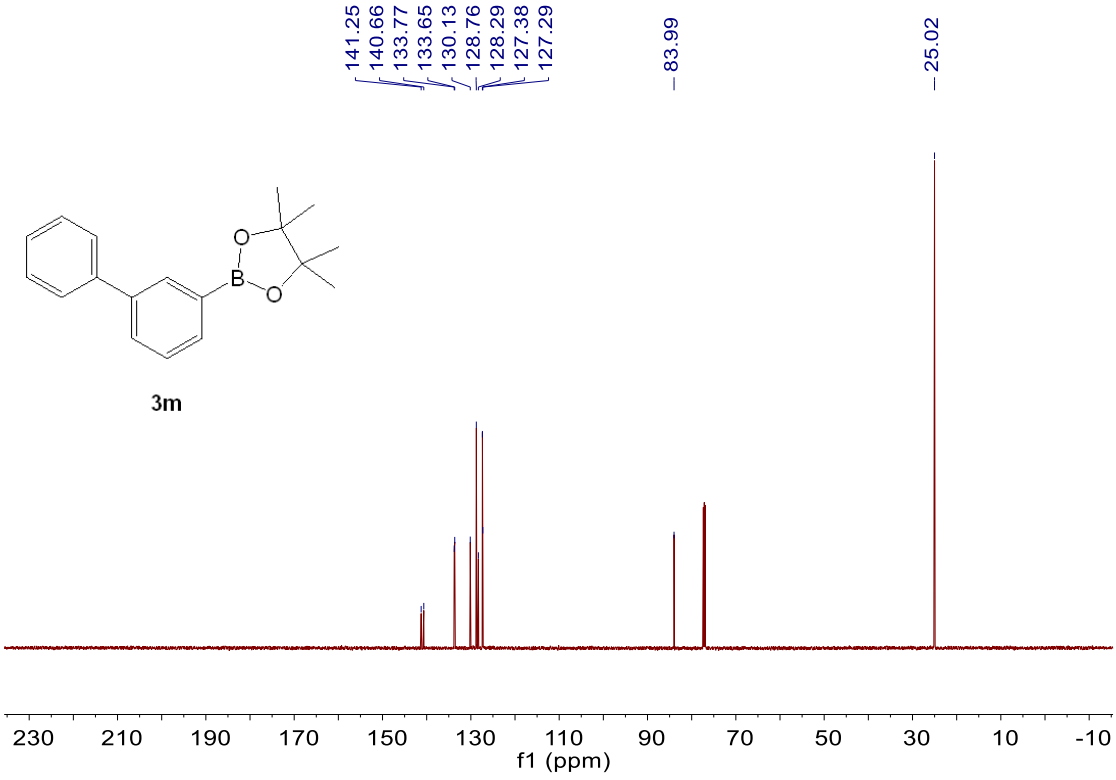


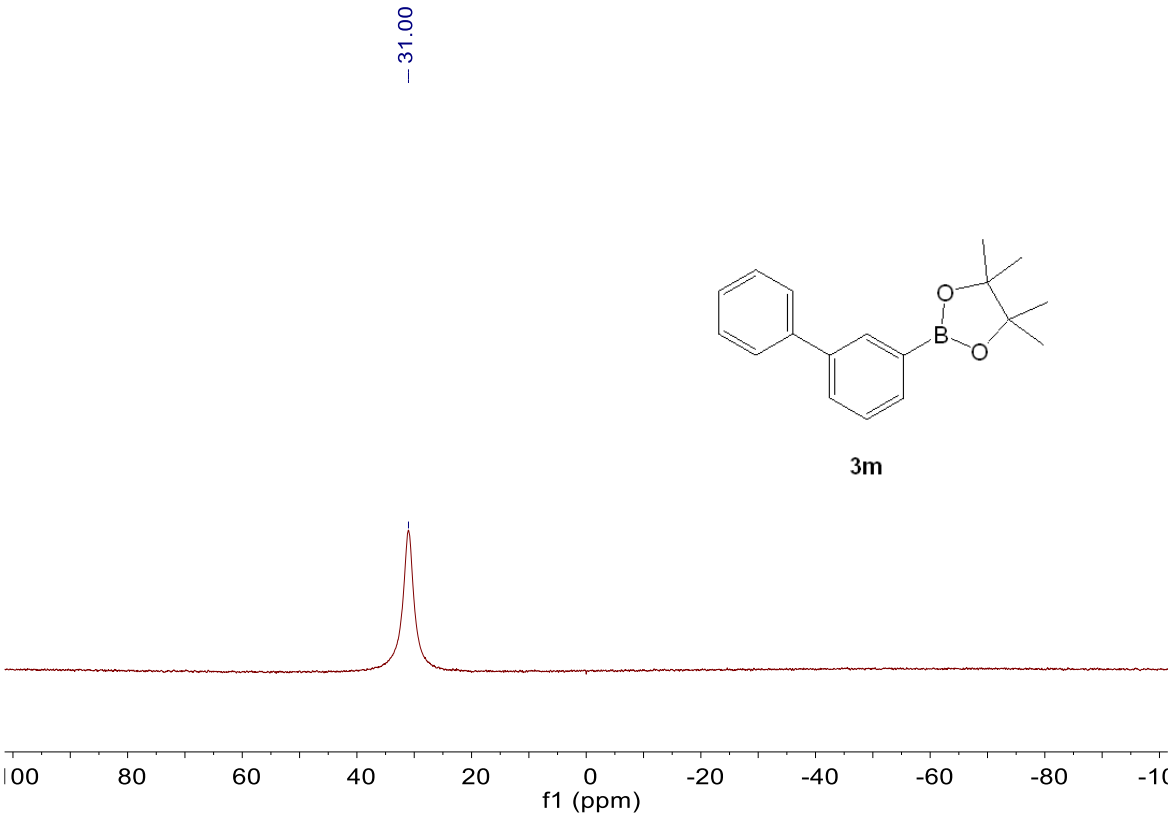




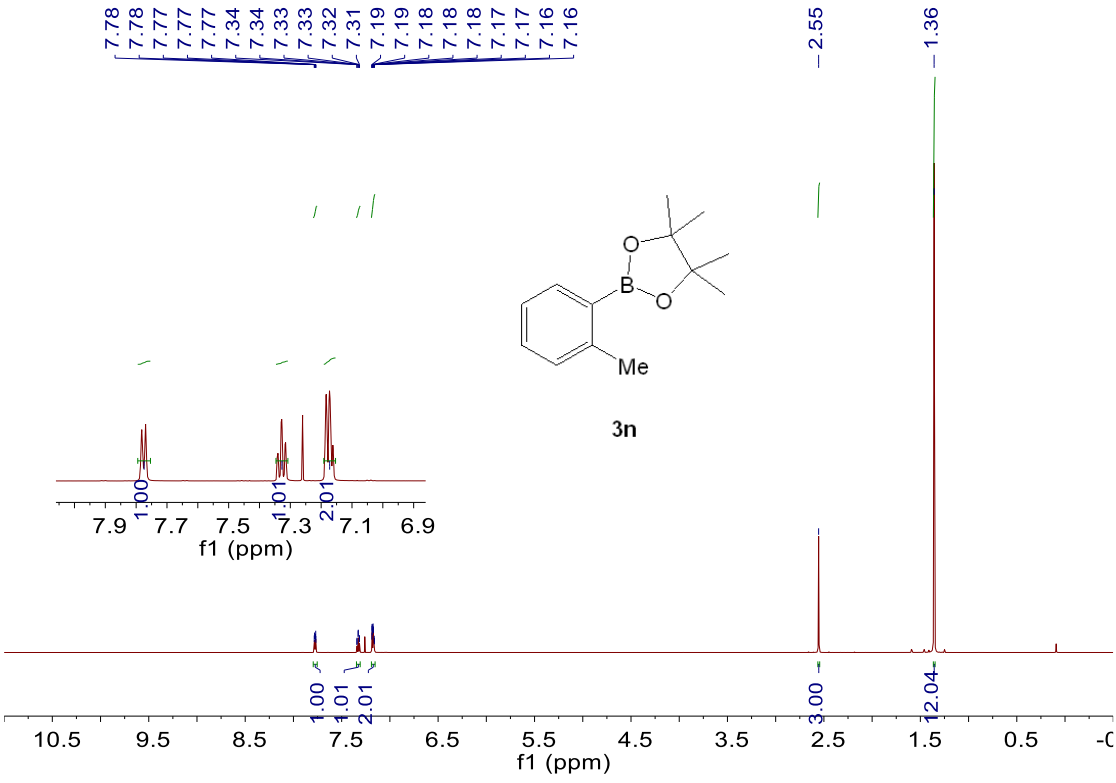
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3l** ($CDCl_3$, rt).

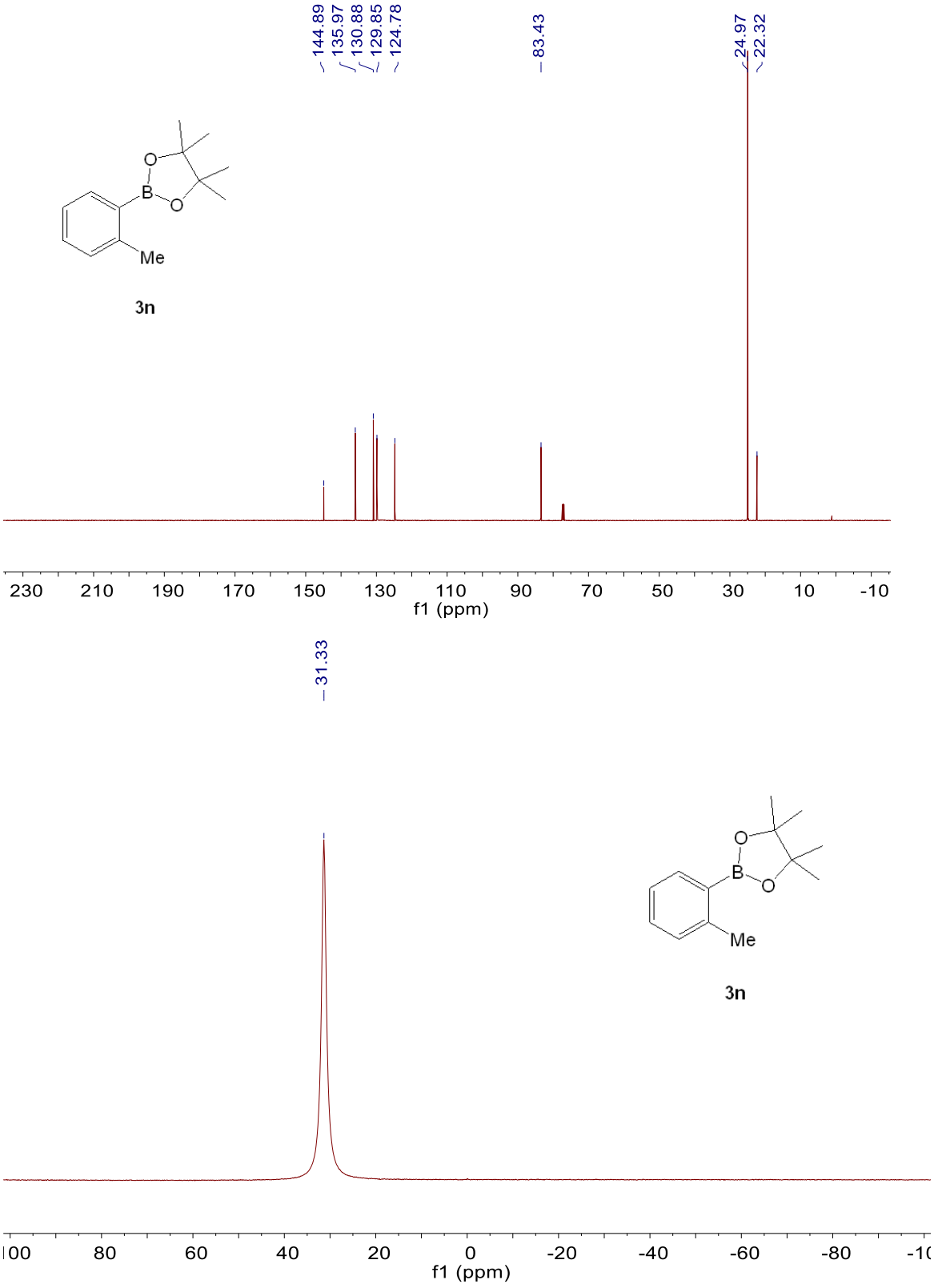

8.07
8.07
8.07
7.82
7.82
7.81
7.80
7.72
7.71
7.71
7.71
7.70
7.70
7.70
7.70
7.65
7.65
7.64
7.64
7.63
7.48
7.47
7.45
7.44
7.44
7.43
7.36
7.36
7.36
7.35
7.35
7.34
7.33
1.37
1.00
1.01
1.02
2.02
3.06
1.01
12.02
f1 (ppm)
3m


141.25
140.66
133.77
133.65
130.13
128.76
128.29
127.38
127.29
83.99
25.02
f1 (ppm)
3m

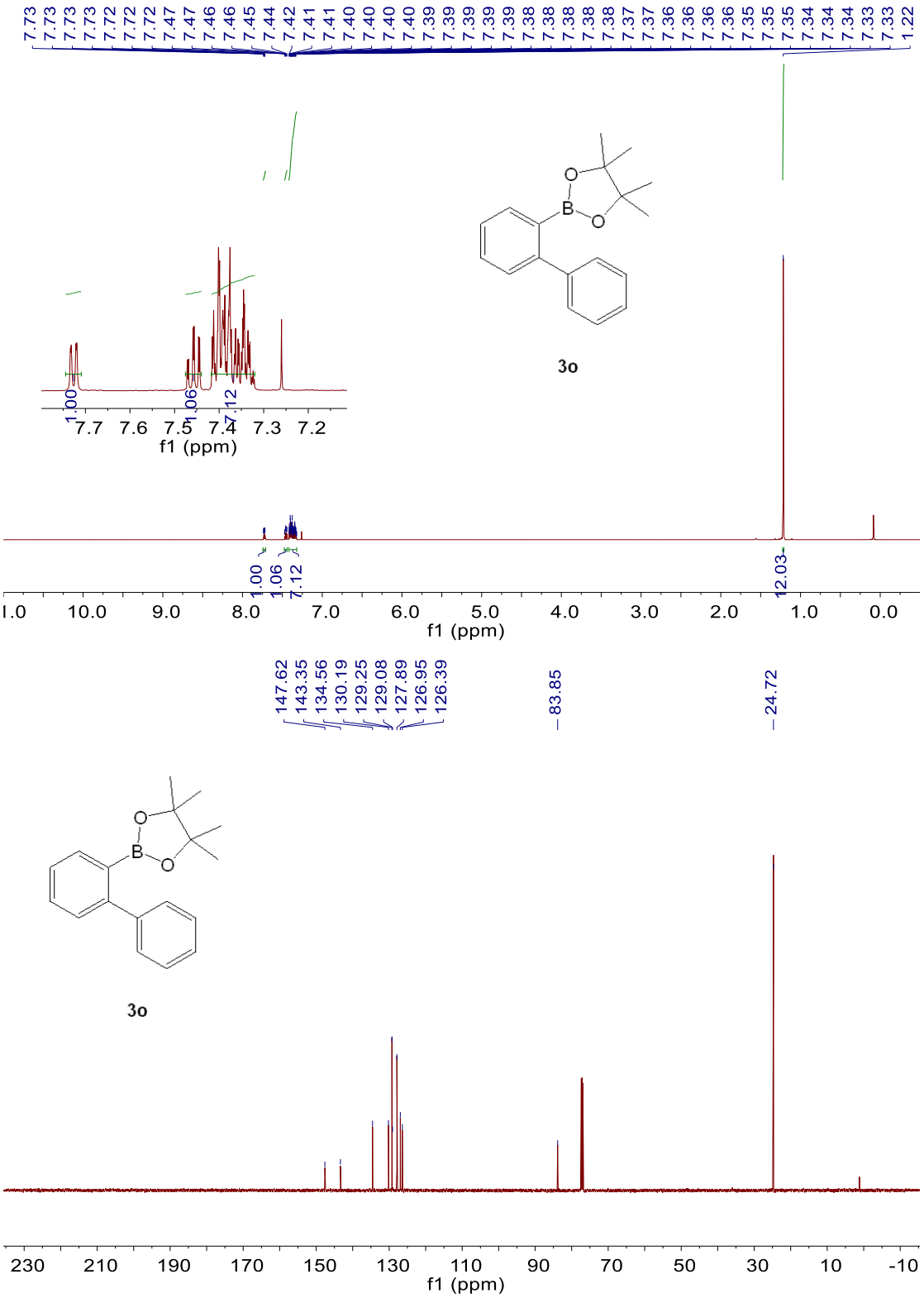


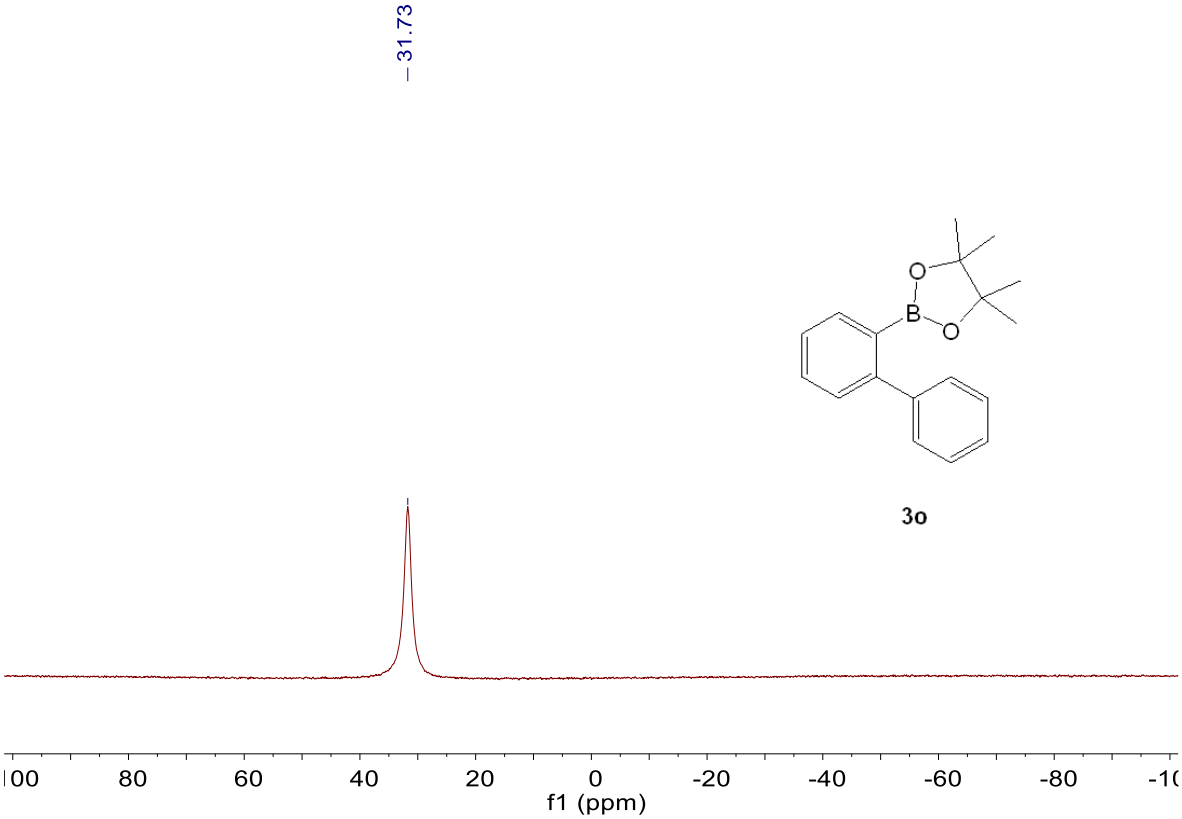
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3m** ($CDCl_3$, rt).



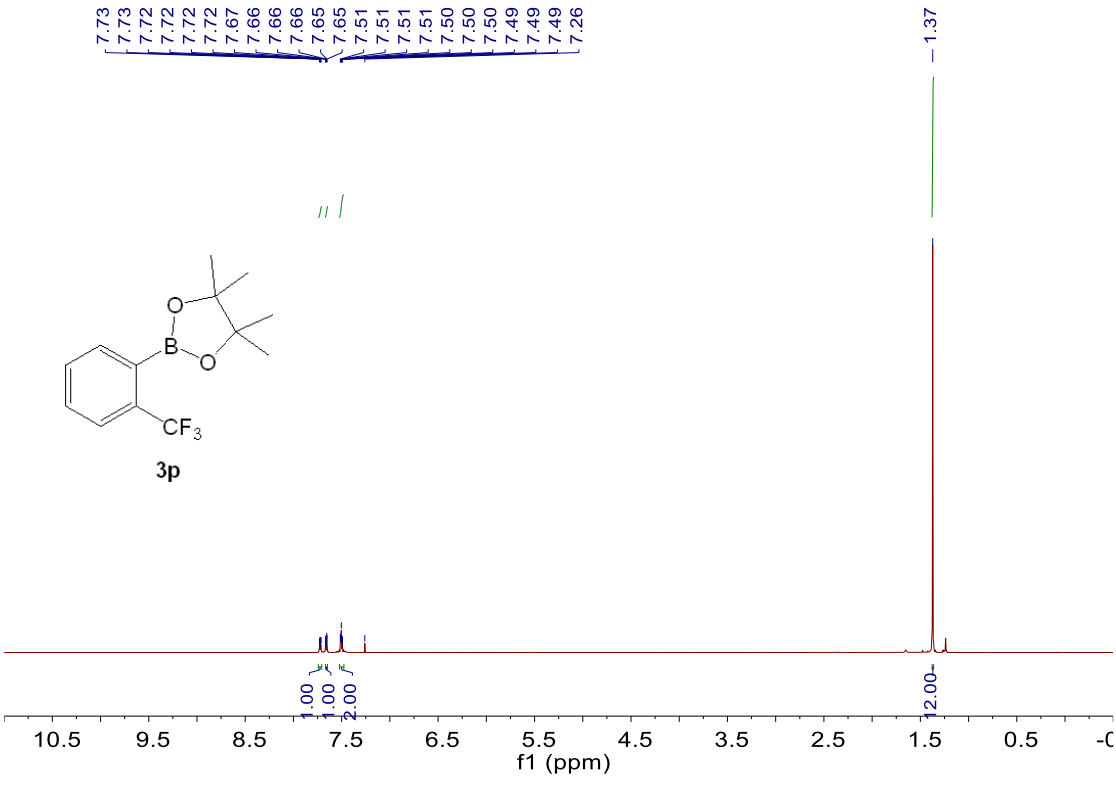


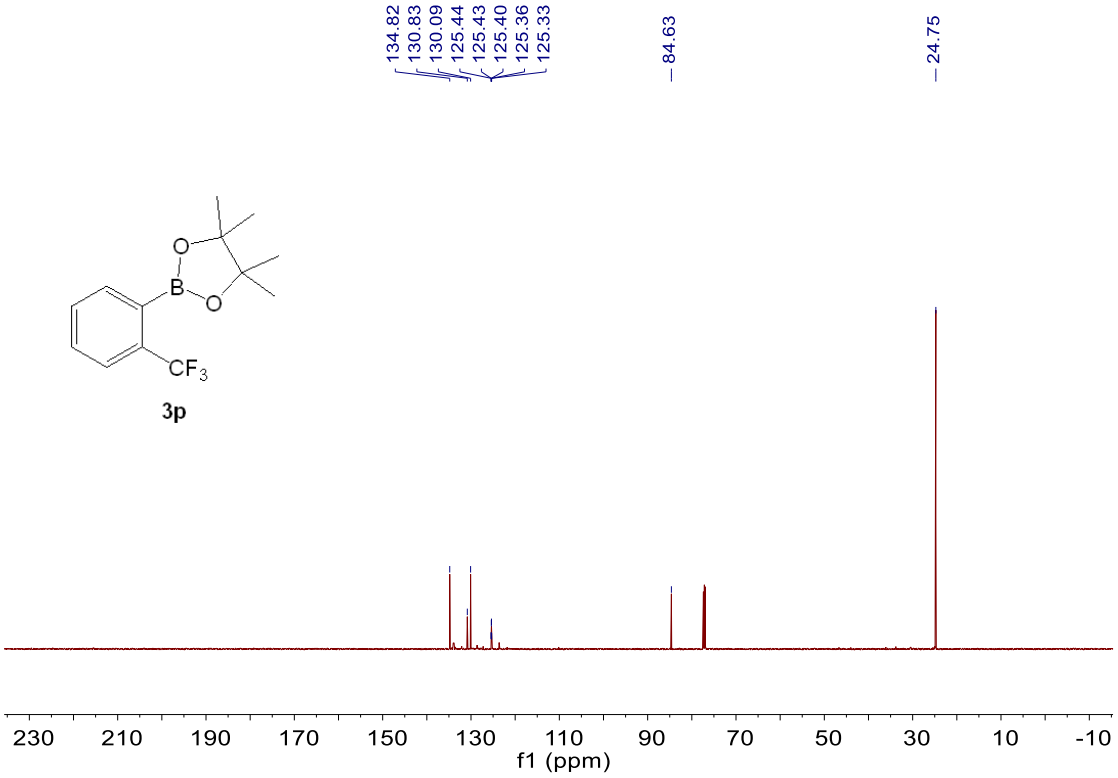
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3n** ($CDCl_3$, rt).


7.73 7.73 7.73 7.73 7.72 7.72 7.72 7.47 7.47 7.46 7.46 7.45 7.44 7.42 7.41 7.41 7.40 7.40 7.40 7.39 7.39 7.39 7.39 7.39 7.38 7.38 7.38 7.38 7.37 7.37 7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.33 7.33 1.22
O
B
O
3o
1.00 1.06 7.12
7.7 7.6 7.5 7.4 7.3 7.2
f1 (ppm)
1.00 1.06 7.12 12.03
1.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)
147.62 143.35 134.56 130.19 129.25 129.08 127.89 126.95 126.39 83.85 24.72
O
B
O
3o
230 210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)

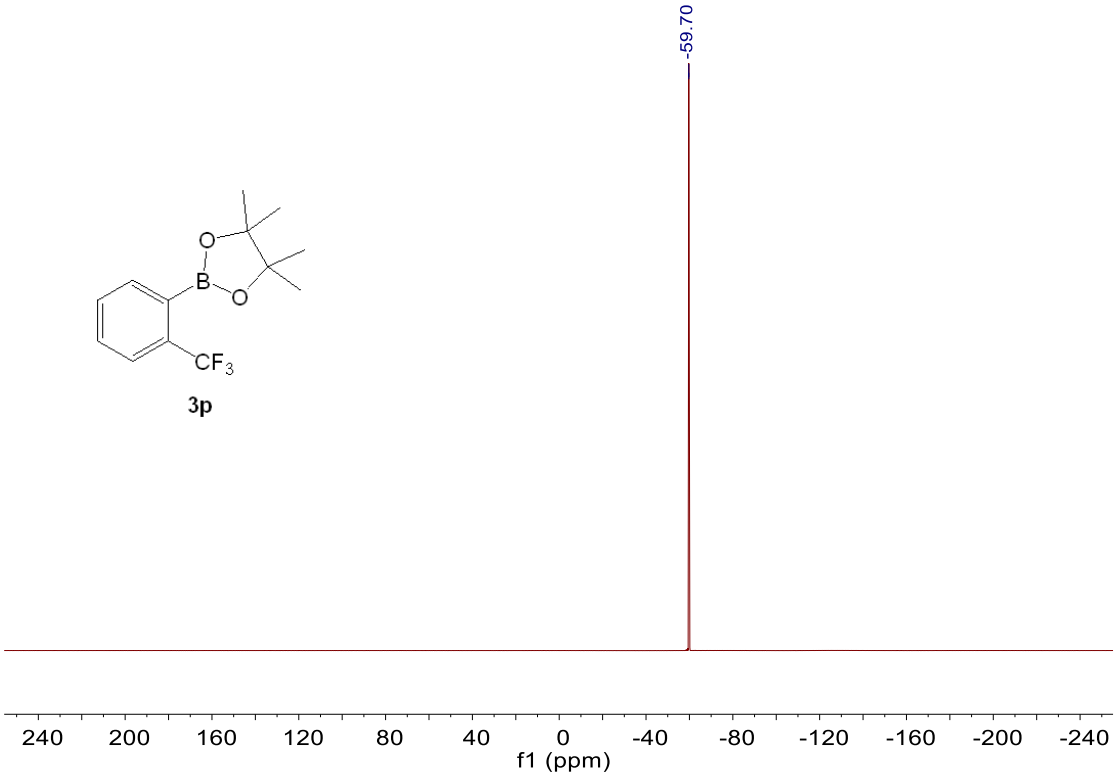


^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3o** ($CDCl_3$, rt).

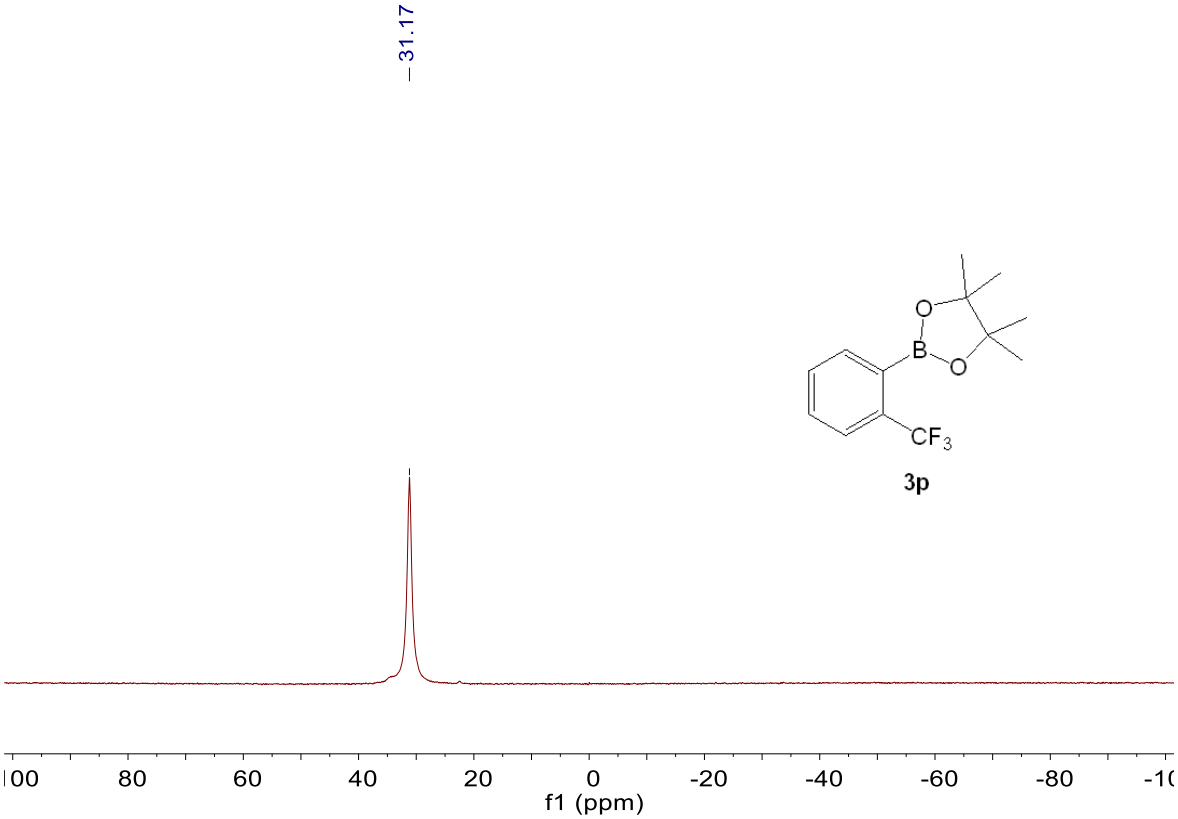



134.82
130.83
130.09
125.44
125.43
125.40
125.36
125.33
84.63
24.75
O
B
O
CF3
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

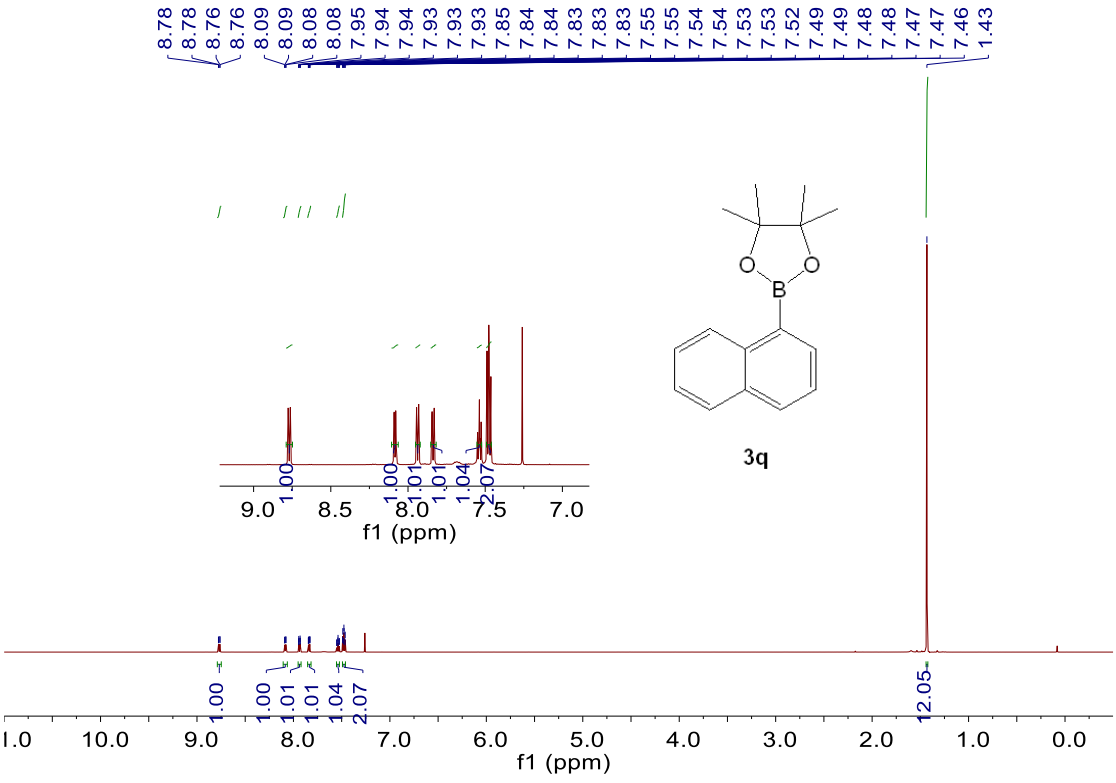
3p

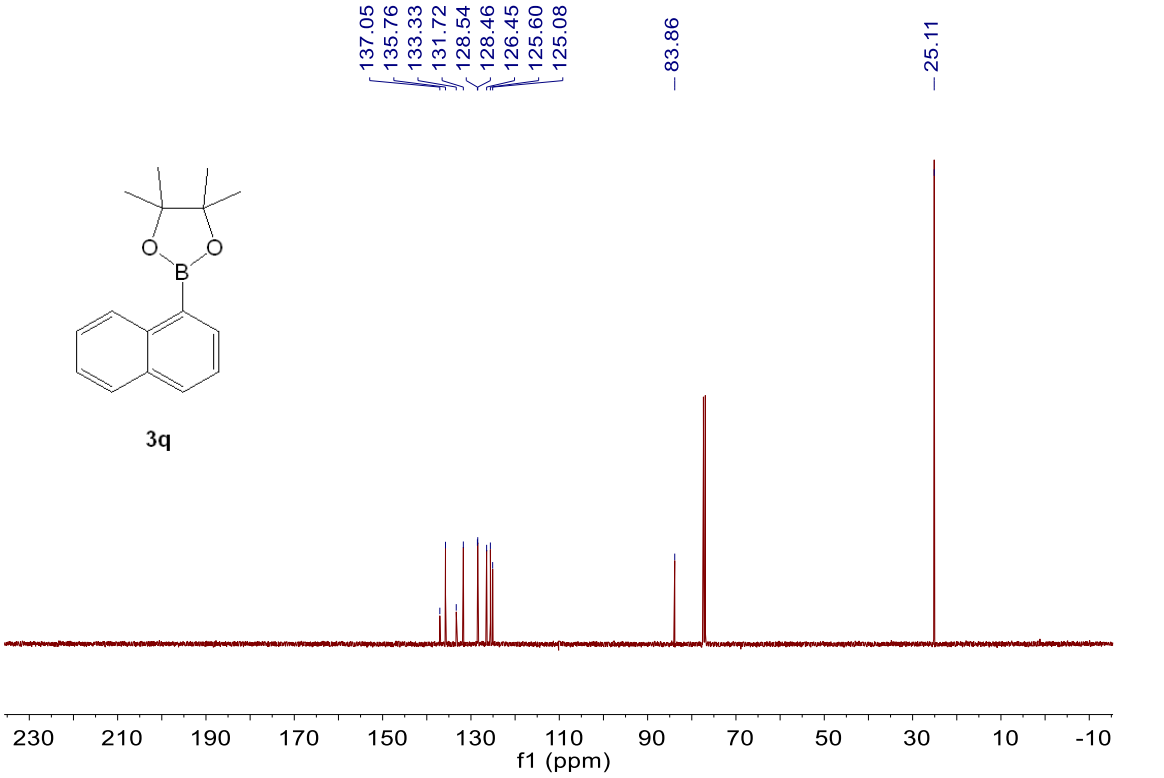

-59.70
O
B
O
CF3
240
200
160
120
80
40
0
-40
-80
-120
-160
-200
-240
f1 (ppm)

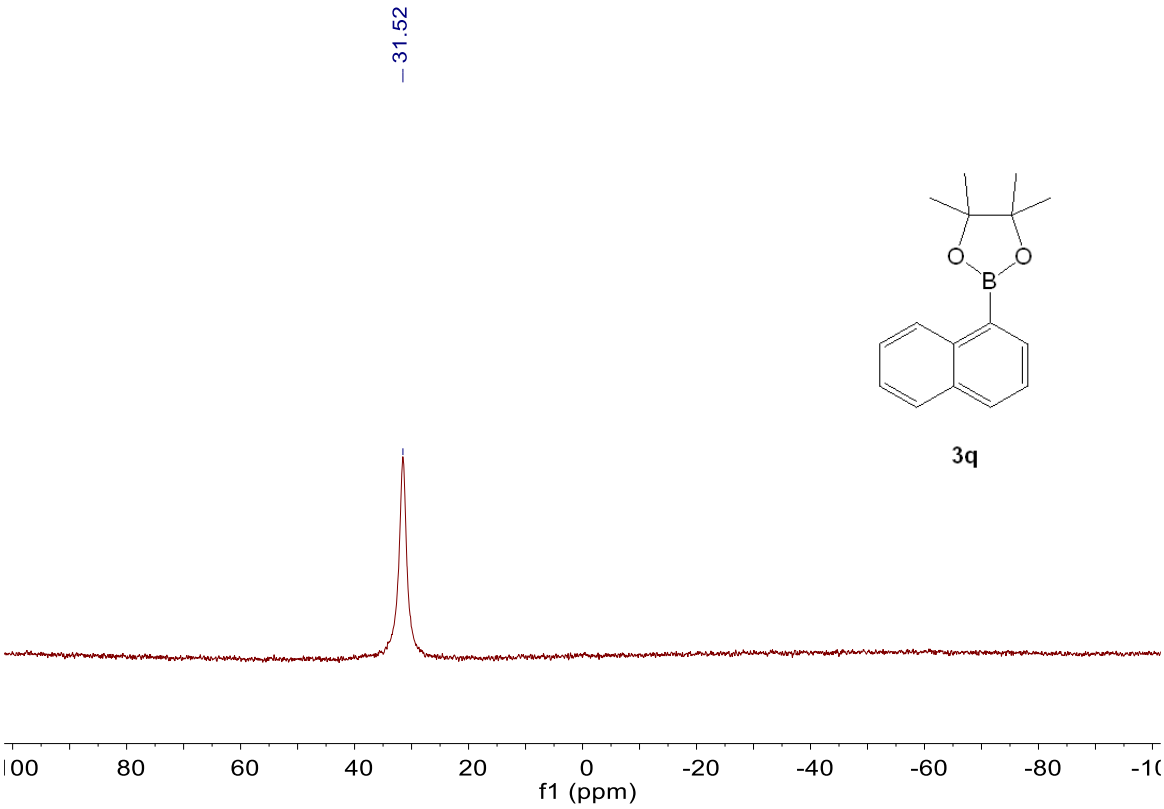
3p



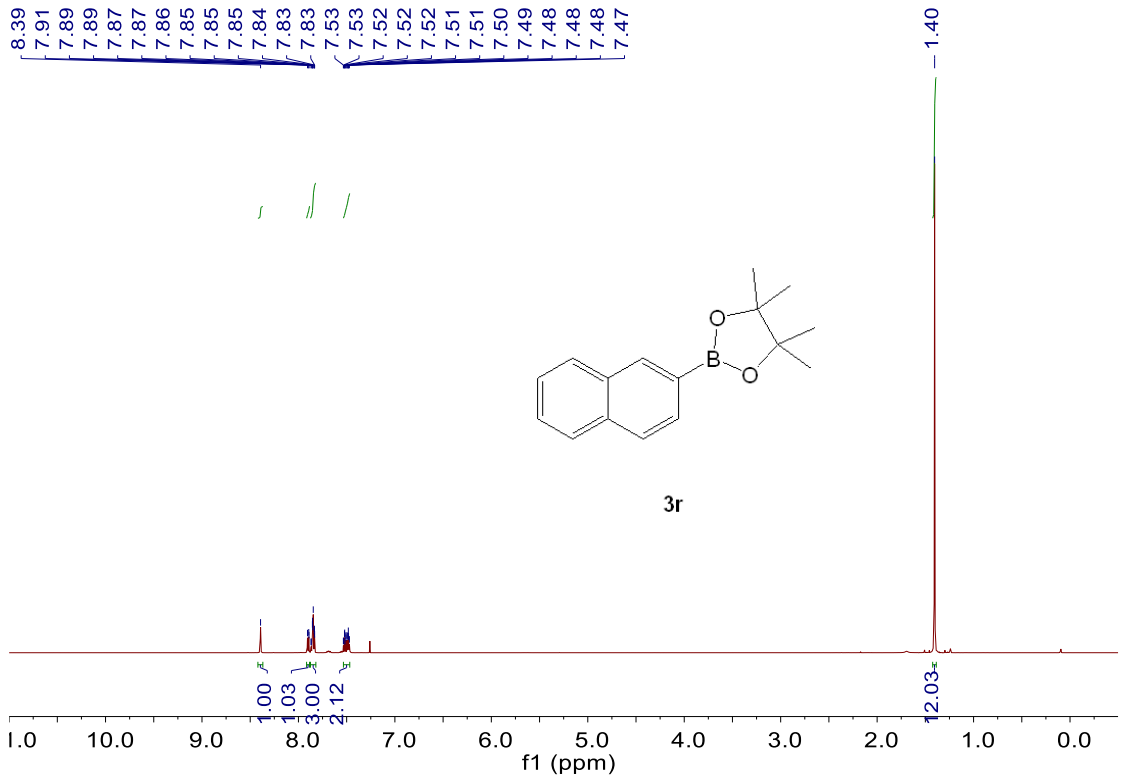
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz), ^{19}F{^{1}H} NMR (376 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3p** ($CDCl_3$, rt).

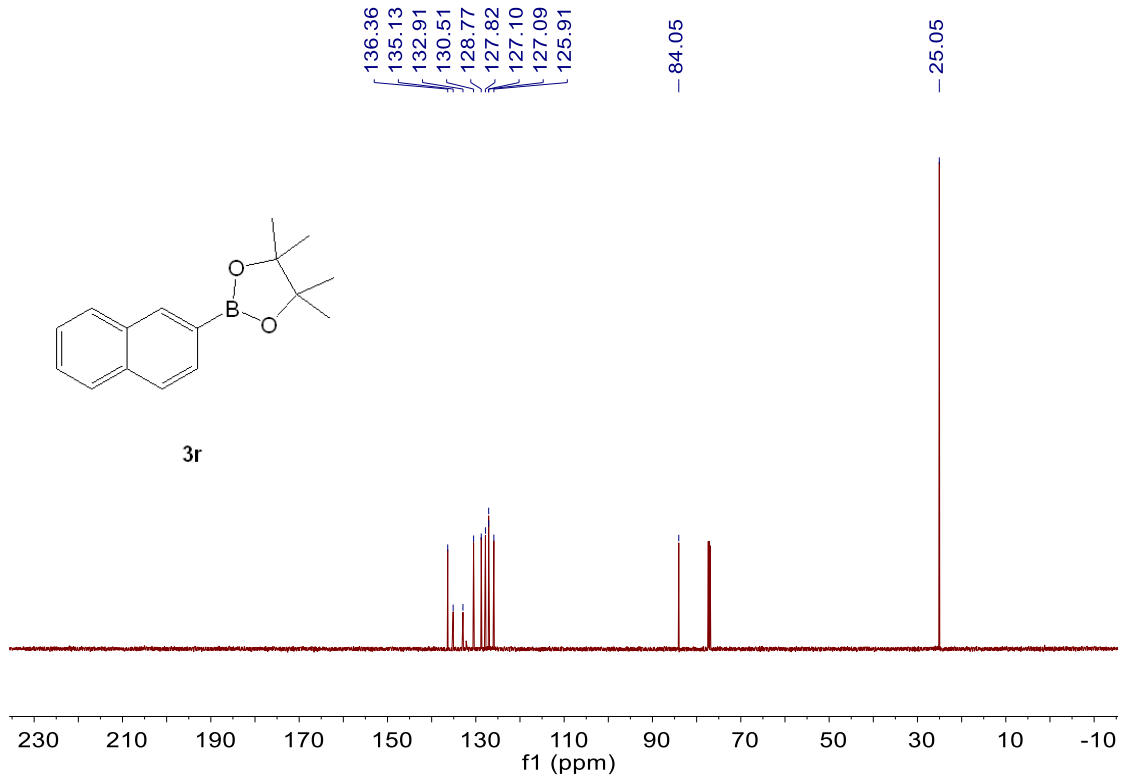


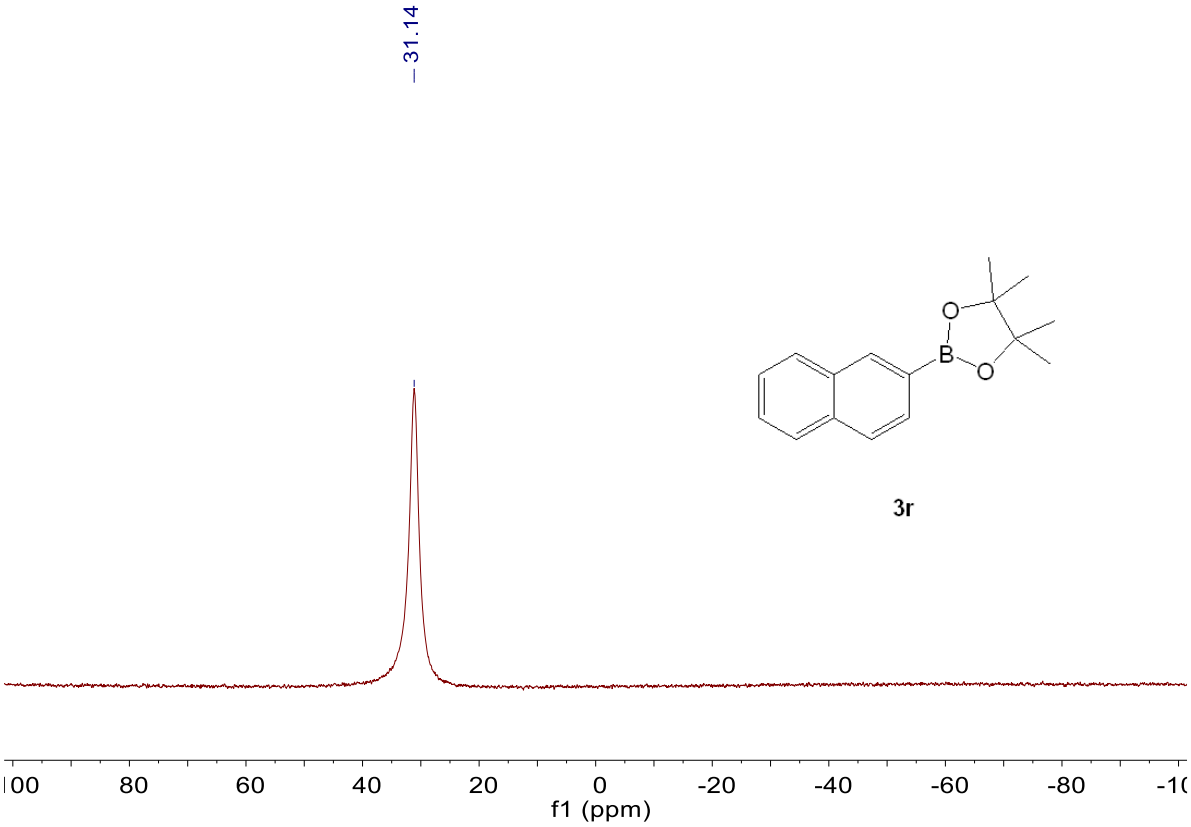




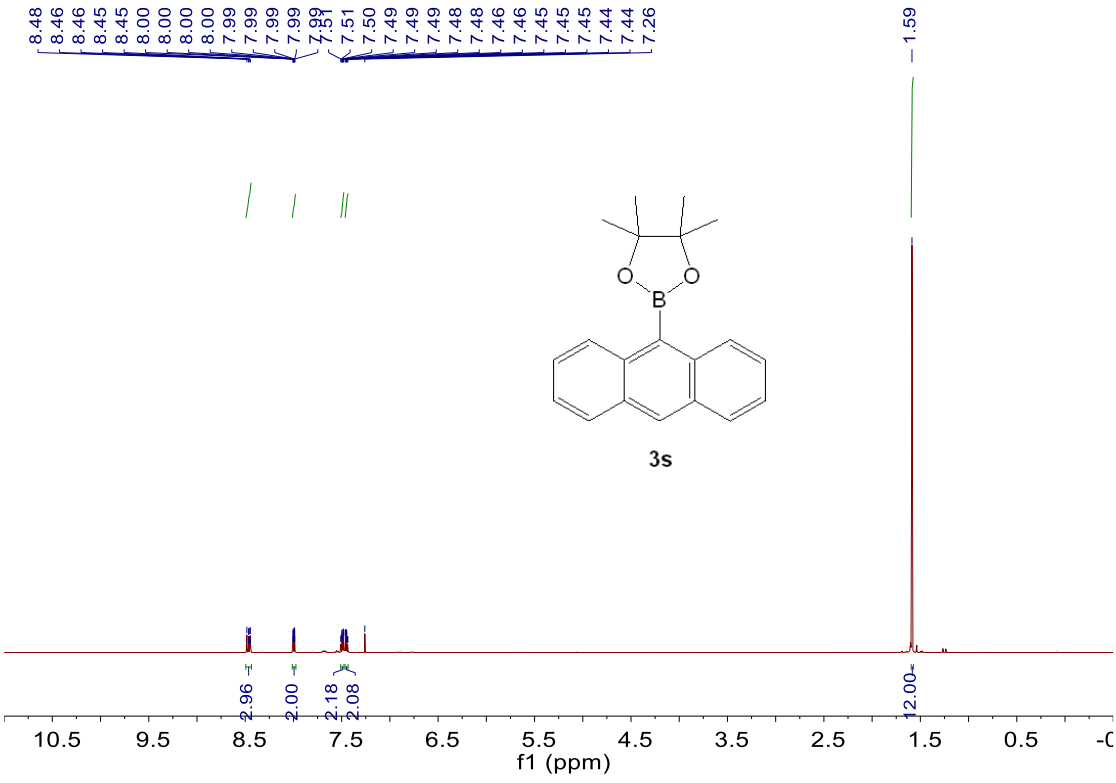
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3q** ($CDCl_3$, rt).

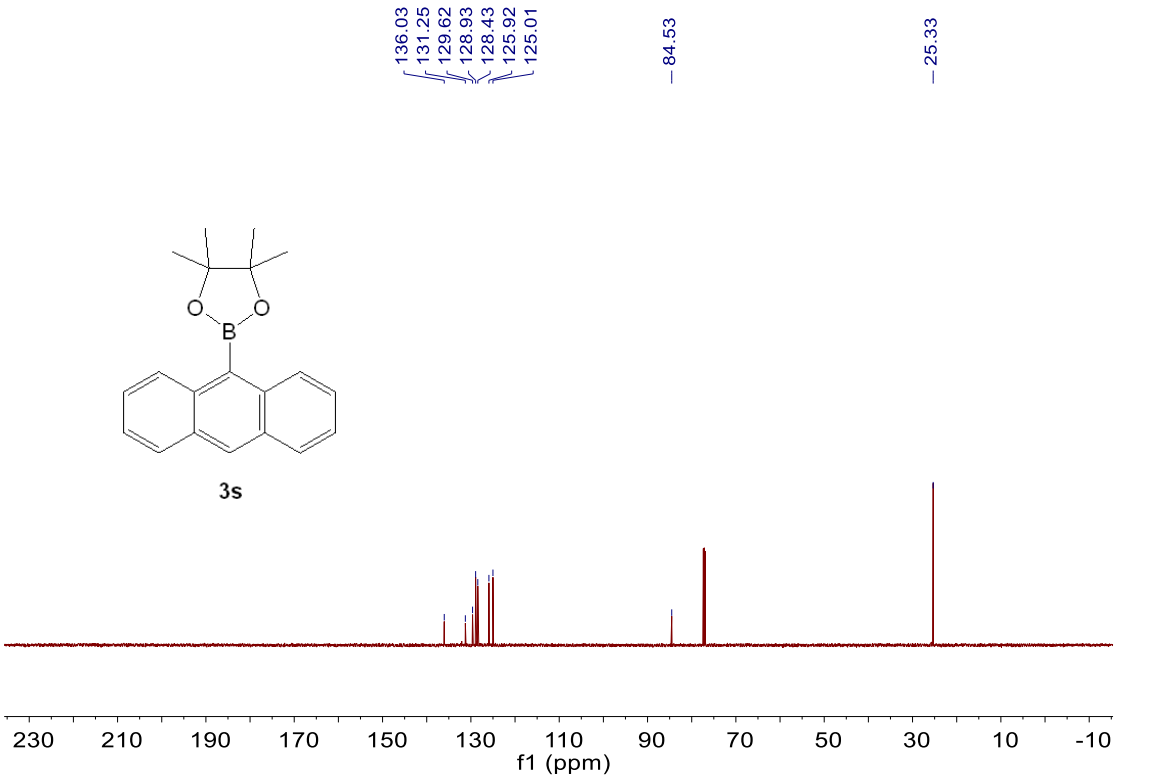

8.39
7.91
7.89
7.89
7.87
7.87
7.86
7.85
7.85
7.85
7.84
7.83
7.83
7.53
7.53
7.52
7.52
7.52
7.51
7.51
7.50
7.49
7.48
7.48
7.48
7.47
1.40
O
B
O
3r
1.00
1.03
3.00
2.12
12.03
f1 (ppm)

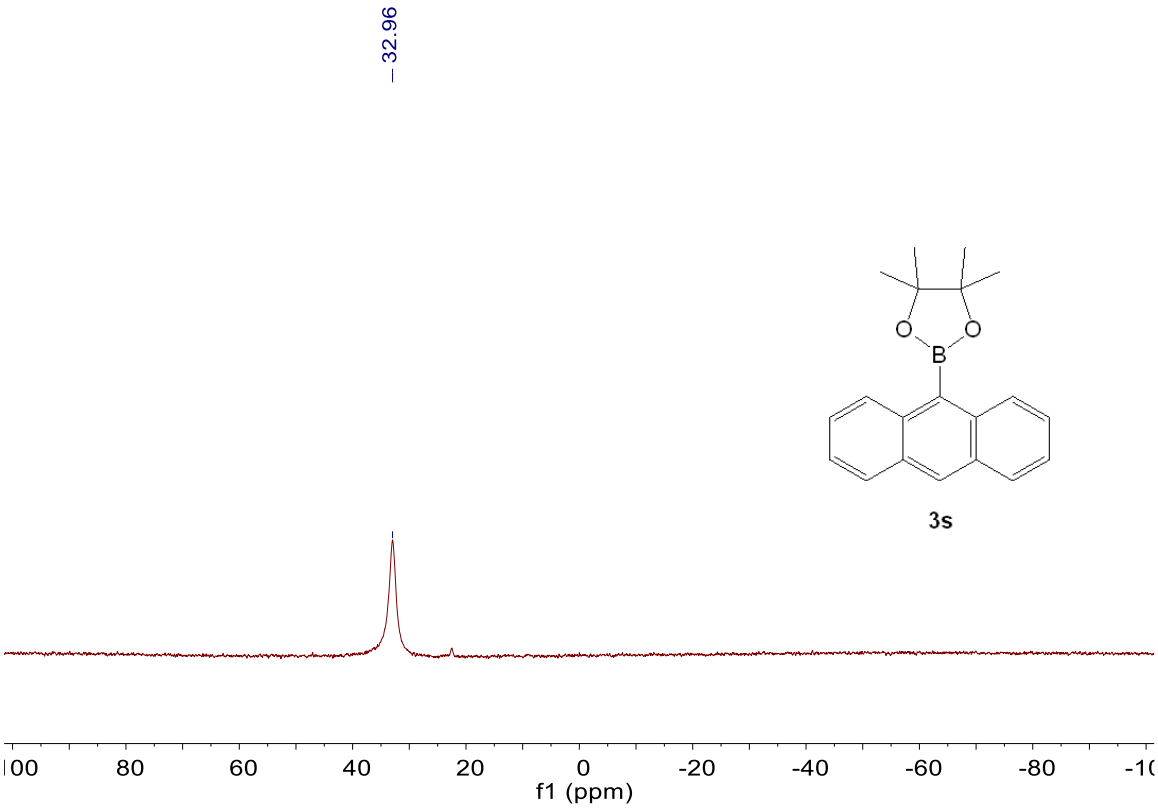

136.36
135.13
132.91
130.51
128.77
127.82
127.10
127.09
125.91
84.05
25.05
O
B
O
3r
f1 (ppm)



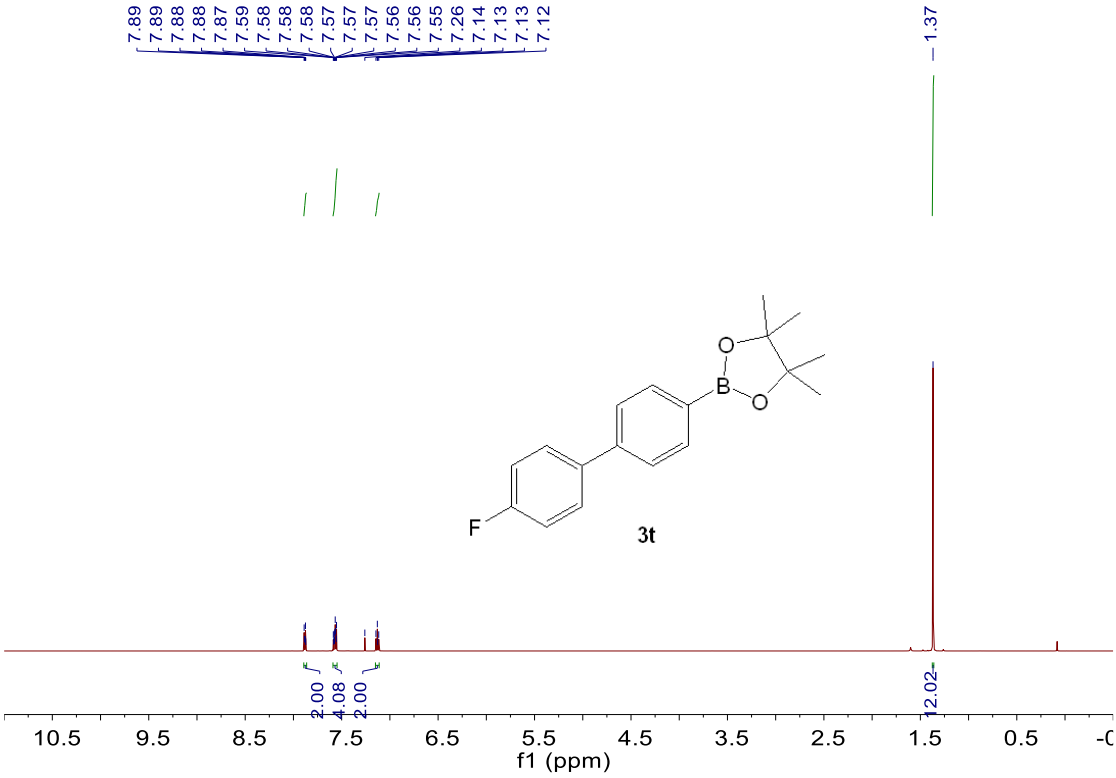
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3r** ($CDCl_3$, rt).

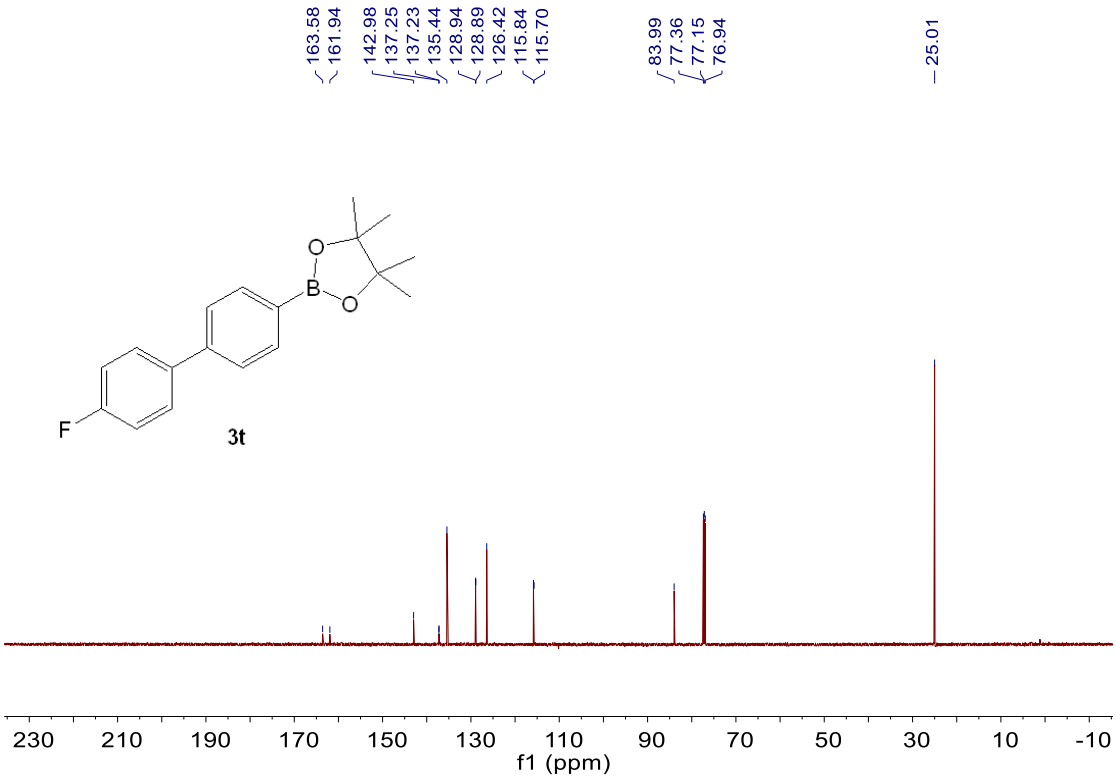


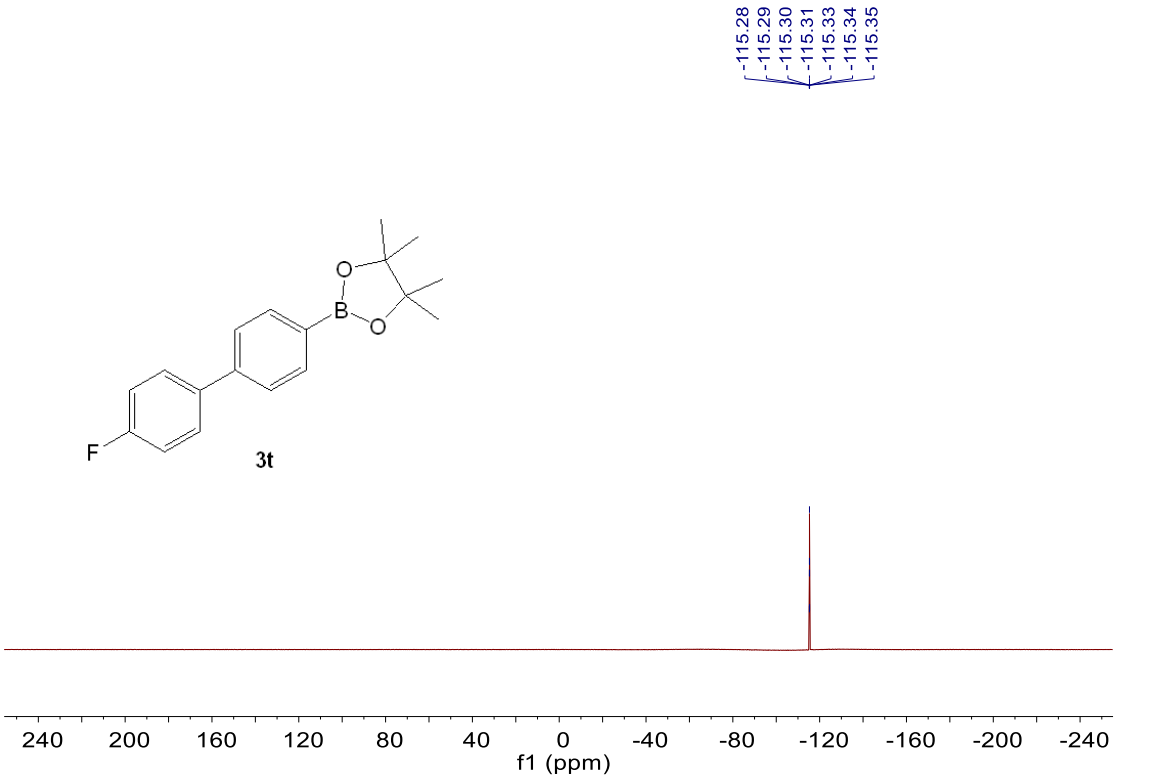


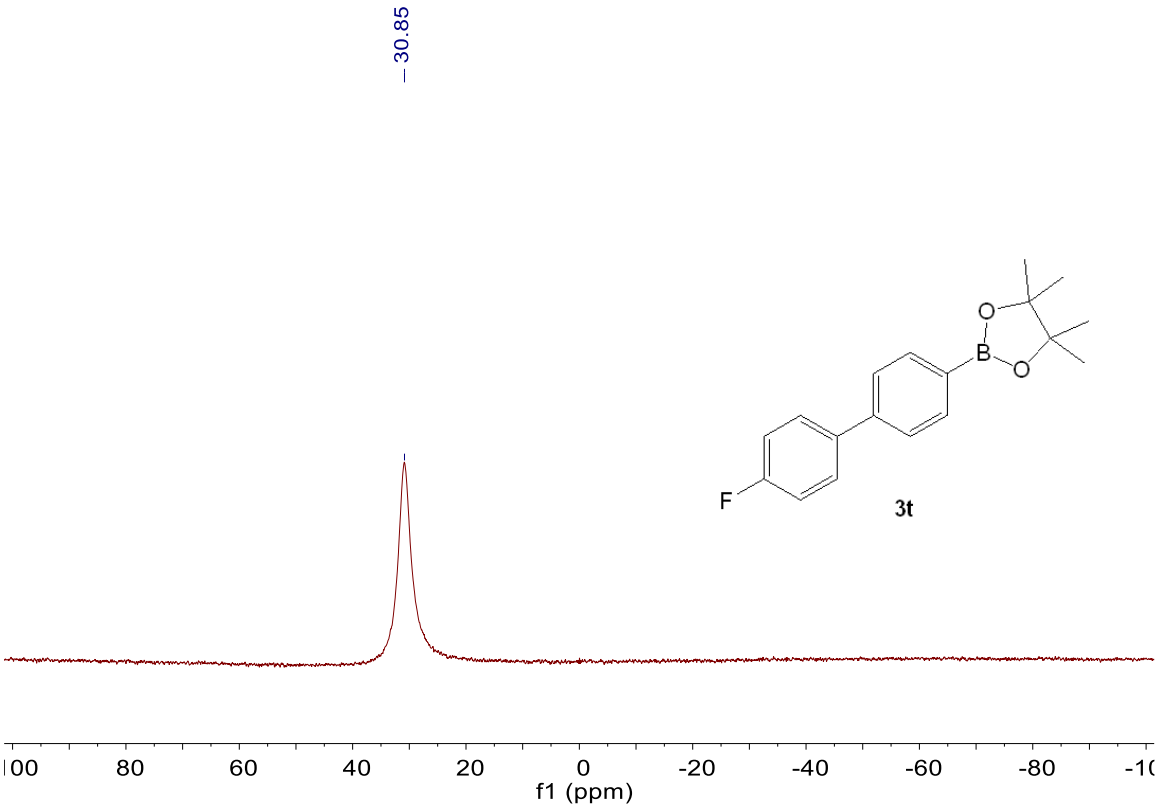


^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3s** ($CDCl_3$, rt).

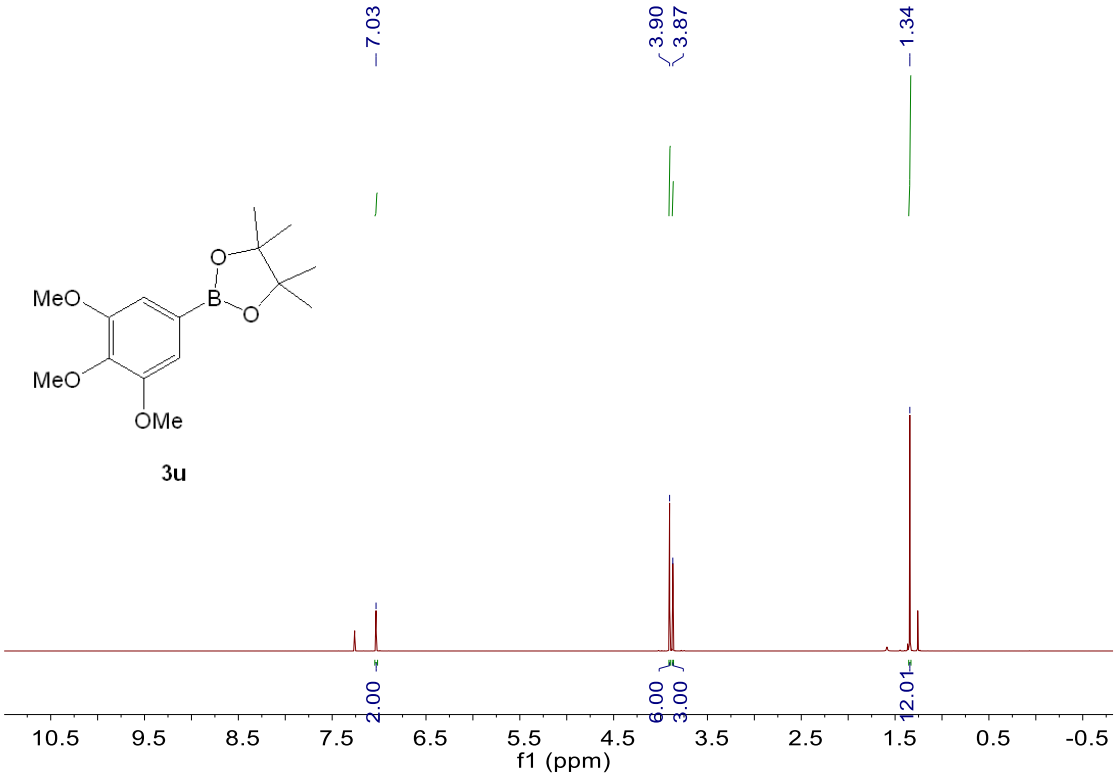

7.89
7.89
7.88
7.88
7.87
7.59
7.58
7.58
7.58
7.57
7.57
7.57
7.56
7.56
7.55
7.26
7.14
7.13
7.13
7.12
1.37
O
B
O
F
3t
2.00
4.08
2.00
12.02
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

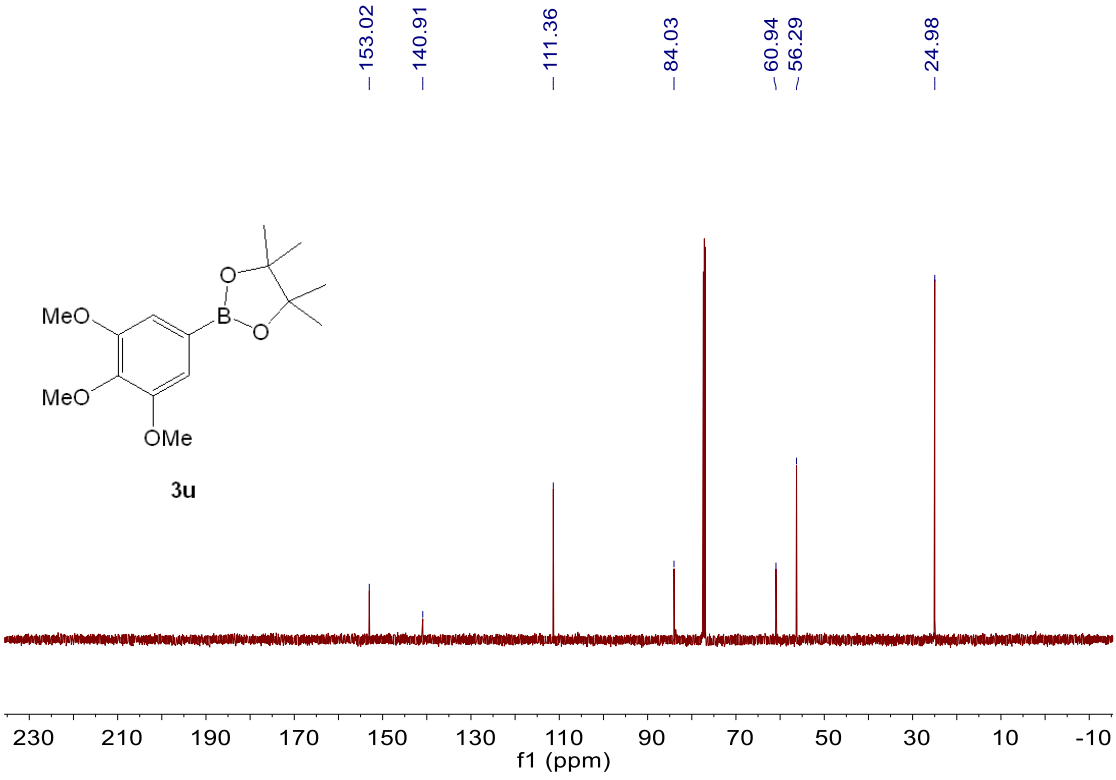

163.58
161.94
142.98
137.25
137.23
135.44
128.94
128.89
126.42
115.84
115.70
83.99
77.36
77.15
76.94
25.01
O
B
O
F
3t
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

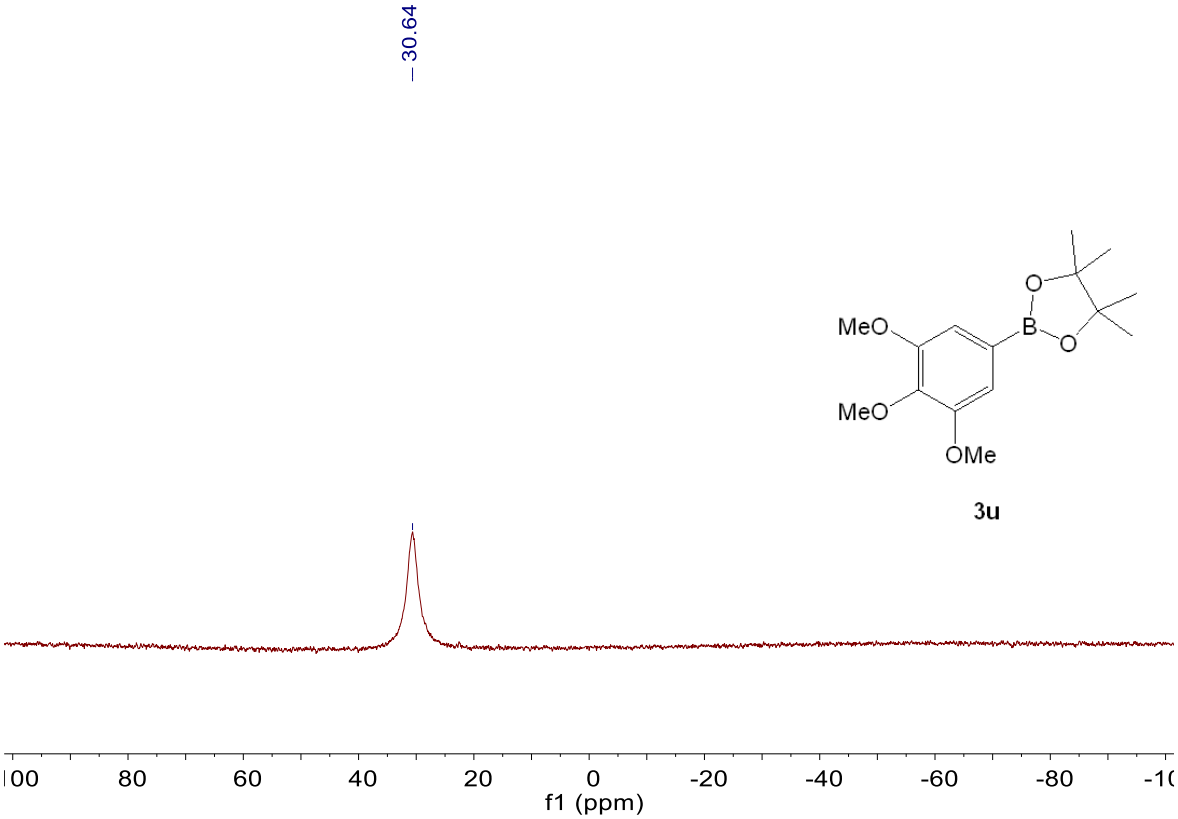




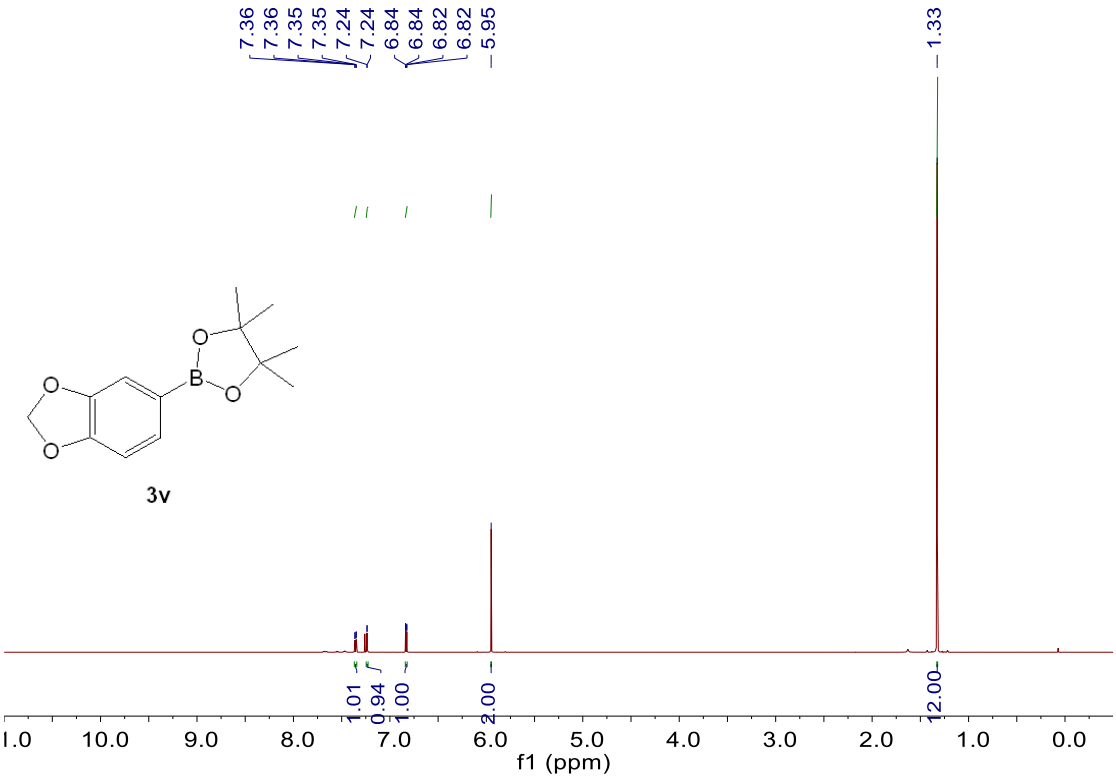
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz), ^{19}F{^{1}H} NMR (376 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3t** ($CDCl_3$, rt).

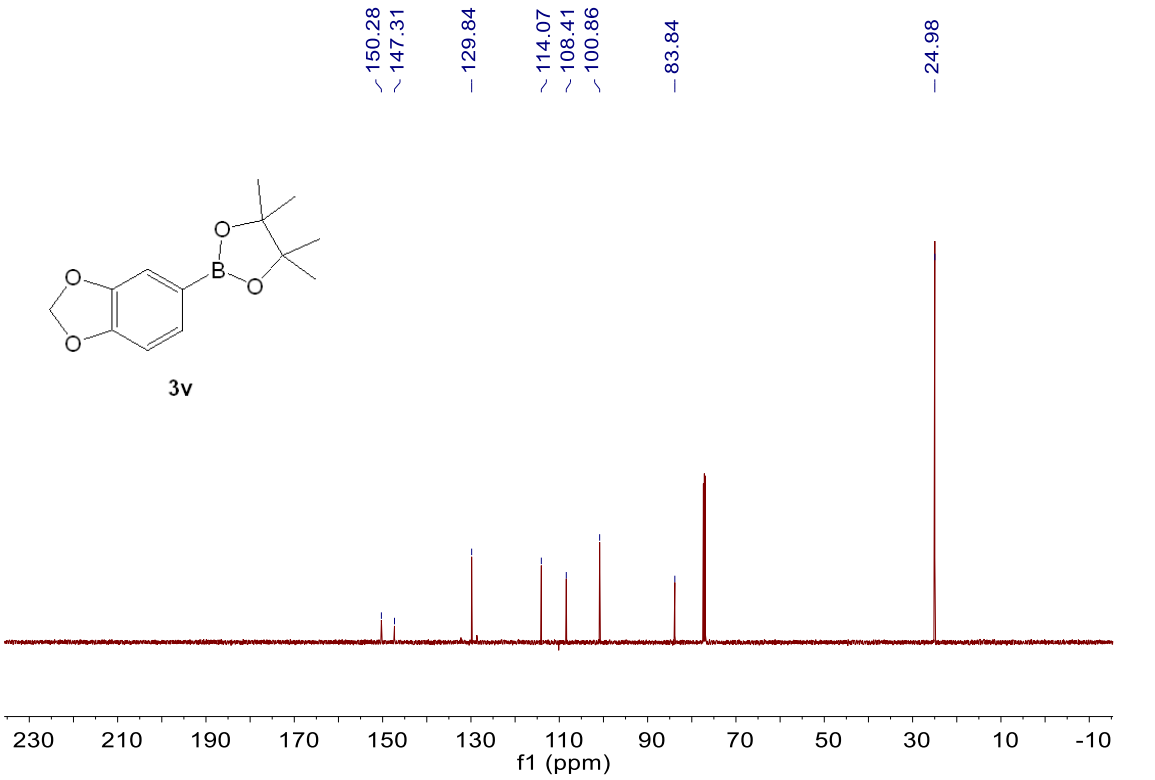

7.03
3.90
3.87
1.34
MeO
MeO
OMe
O
B
O
3u
2.00
6.00
3.00
12.01
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

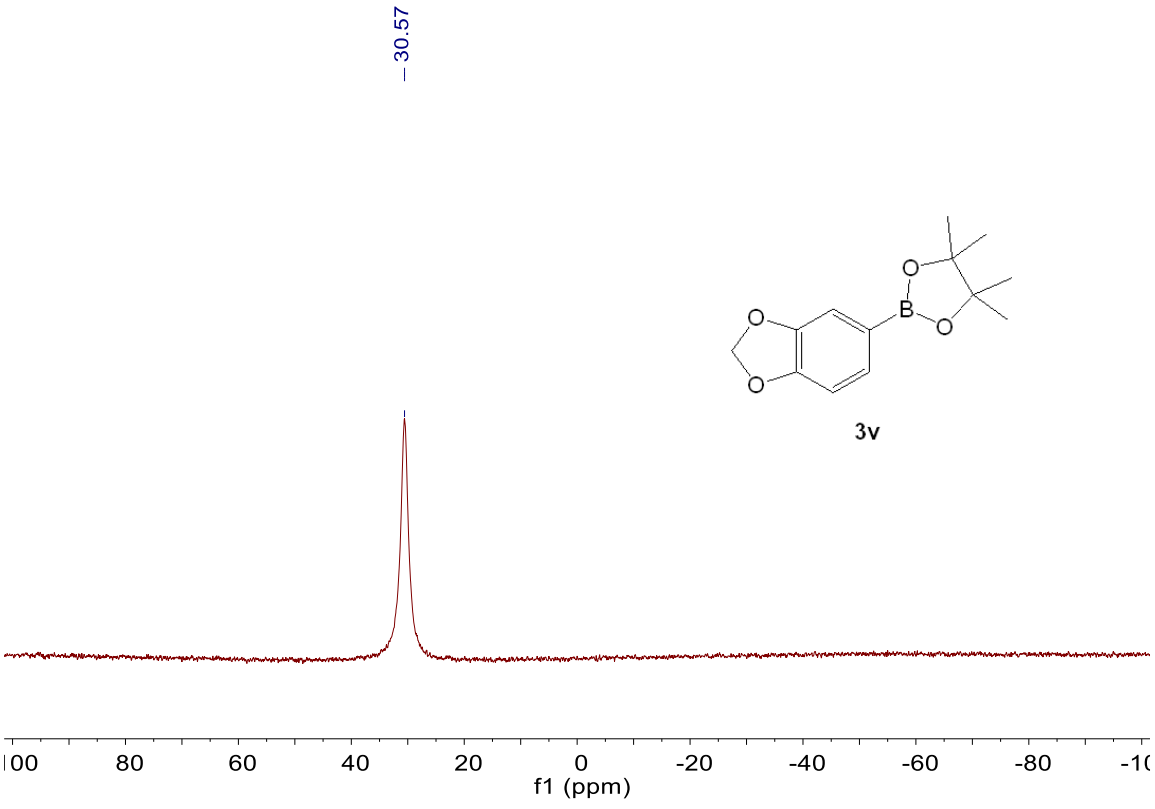

153.02
140.91
111.36
84.03
60.94
56.29
24.98
MeO
MeO
OMe
O
B
O
3u
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)



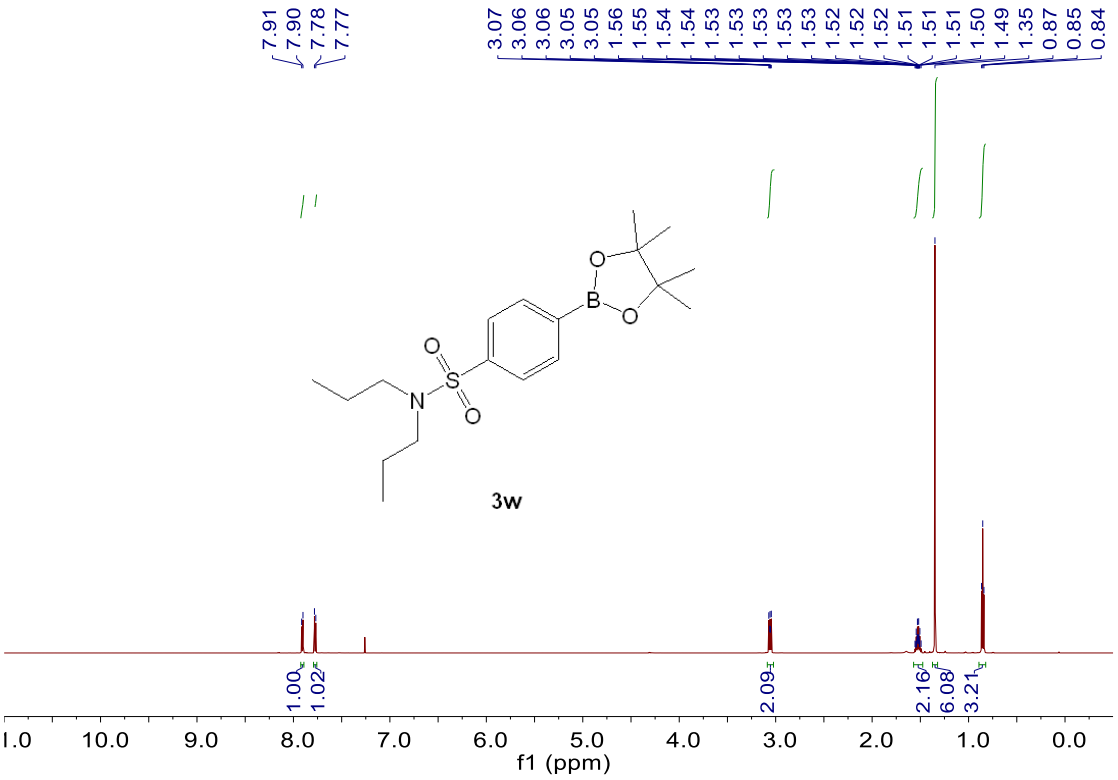
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3u** ($CDCl_3$, rt).

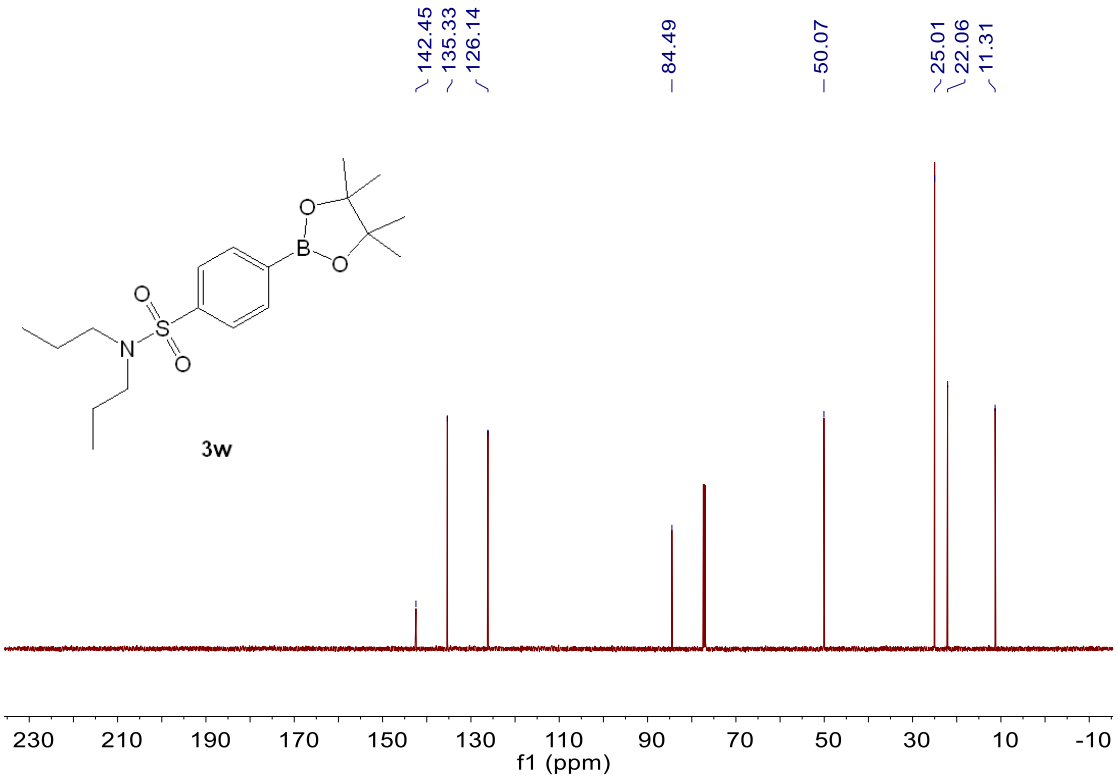


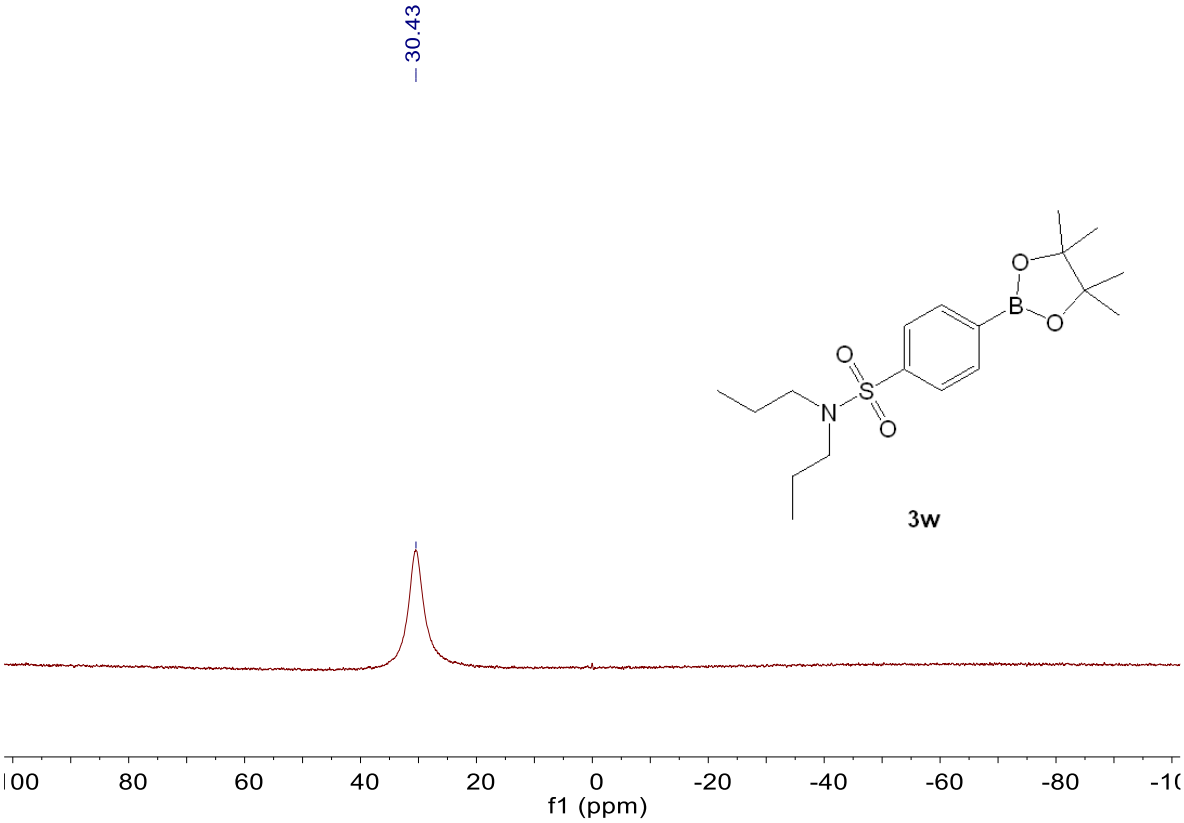




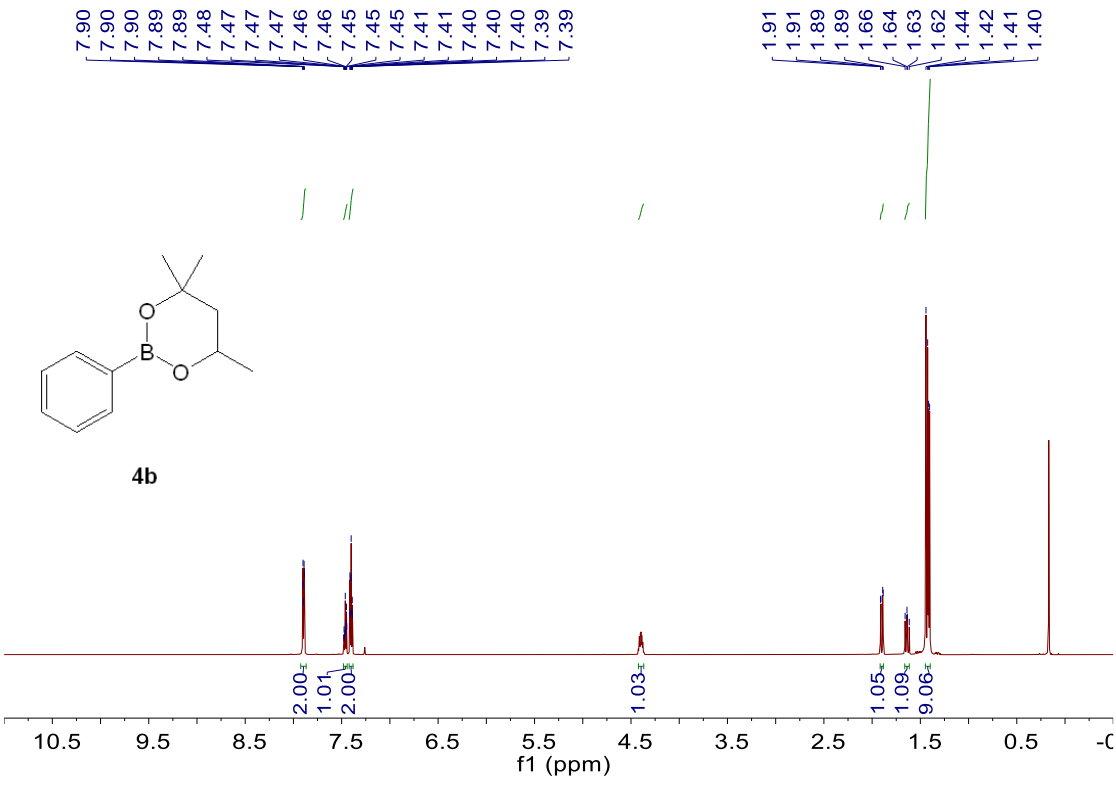
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3v** ($CDCl_3$, rt).

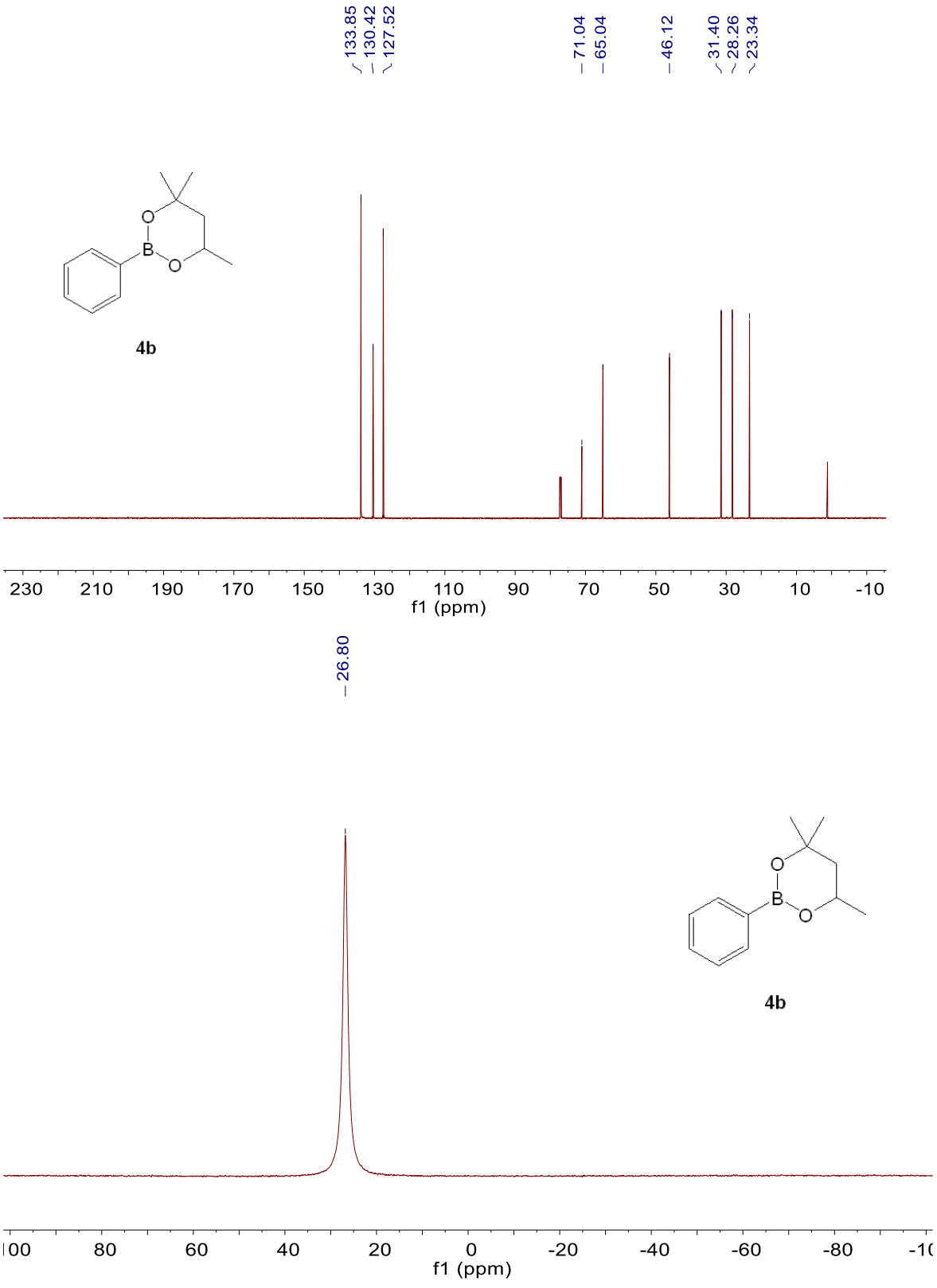

7.91
7.90
7.78
7.77
3.07
3.06
3.06
3.05
3.05
1.56
1.55
1.54
1.54
1.53
1.53
1.53
1.53
1.53
1.52
1.52
1.51
1.51
1.51
1.50
1.49
1.35
0.87
0.85
0.84
3w
1.00
1.02
2.09
2.16
6.08
3.21
f1 (ppm)


142.45
135.33
126.14
84.49
50.07
25.01
22.06
11.31
3w
f1 (ppm)

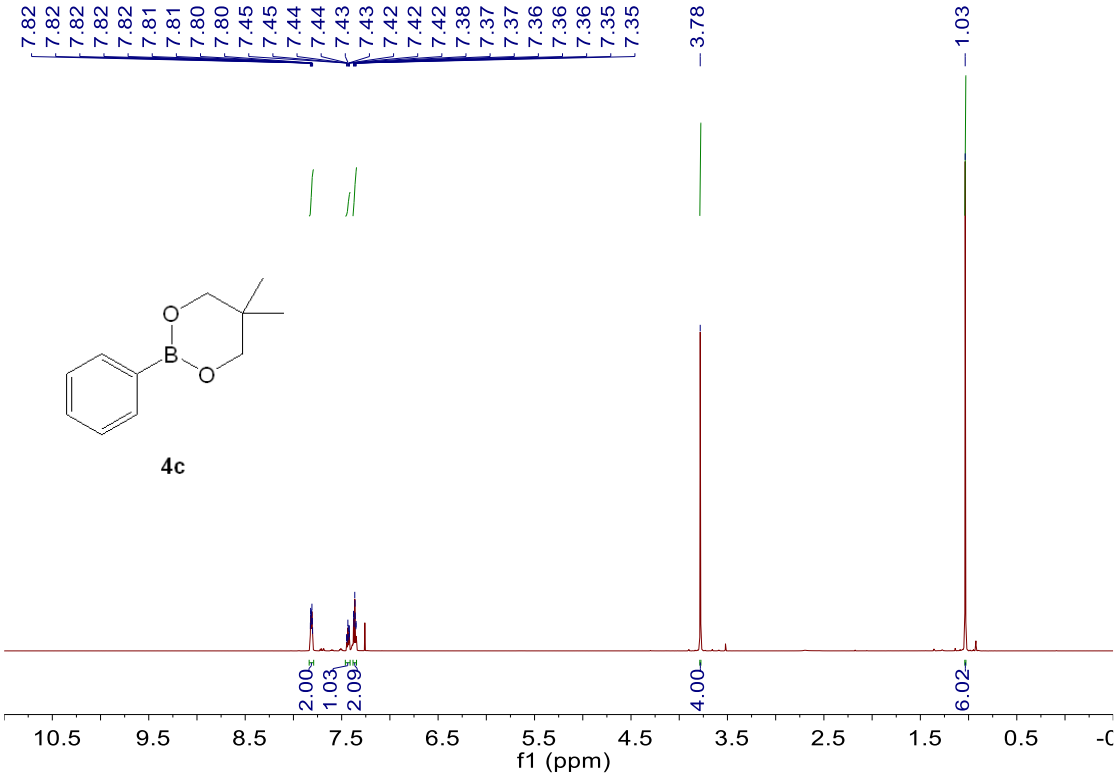


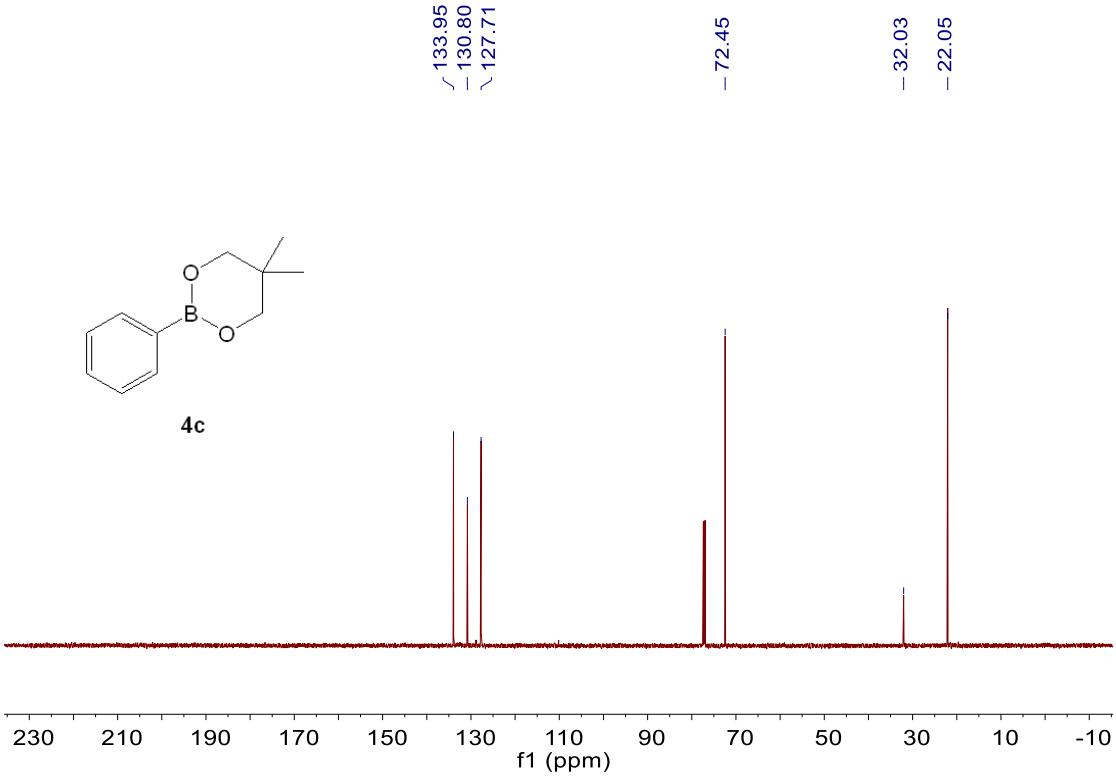
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **3w** ($CDCl_3$, rt).

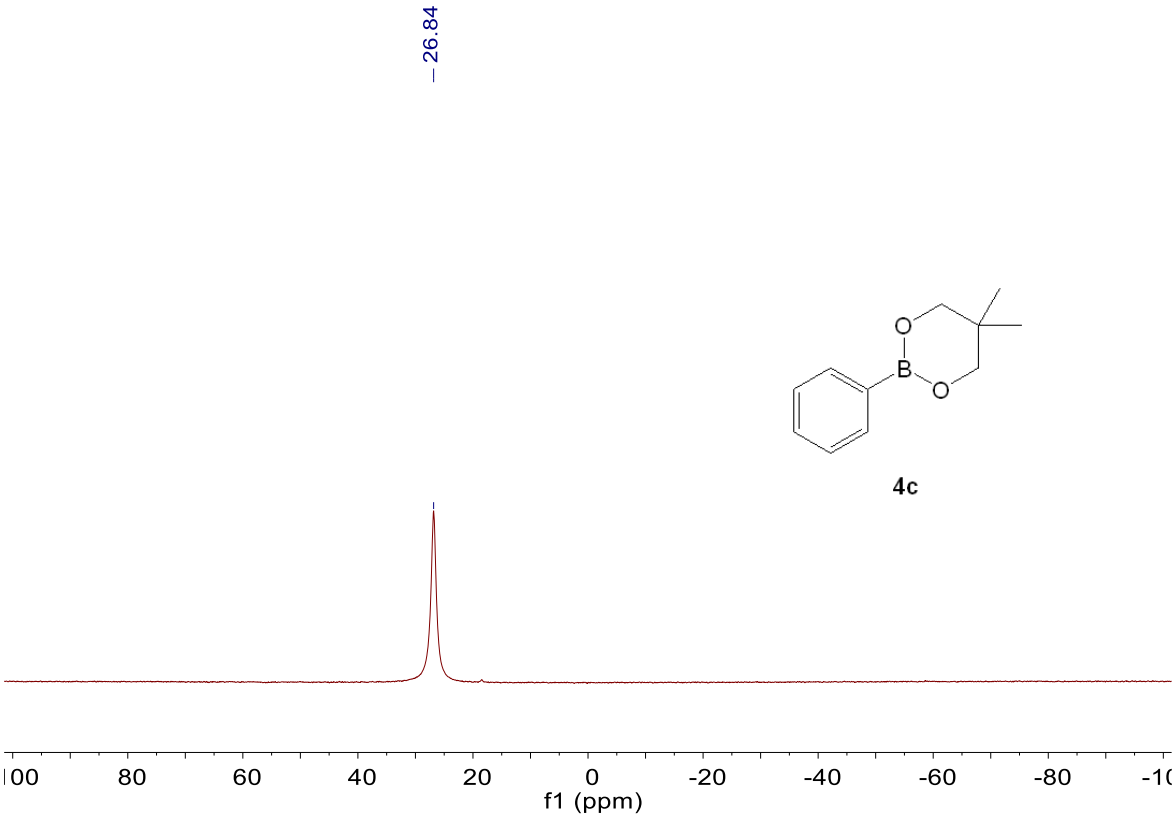




^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **4b** ($CDCl_3$, rt).


7.82
7.82
7.82
7.82
7.82
7.81
7.81
7.80
7.80
7.45
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.42
7.38
7.37
7.37
7.36
7.36
7.36
7.35
7.35
3.78
1.03
O
B
O
4c
2.00
1.03
2.09
4.00
6.02
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


133.95
130.80
127.71
72.45
32.03
22.05
O
B
O
4c
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)



^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{11}B{^{1}H} NMR (192 MHz) spectra of **4c** ($CDCl_3$, rt).

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CHAPTER 4

PPh_3-Assisted Esterification of Acyl Fluorides with Ethers via $C(sp^3)$–O Bond Cleavage Accelerated by TBAT

4-1. Introduction

The C−O bond cleavage in ethers is one of the most fundamental transformations in organic synthesis and has been widely applied in manufacture of fine chemicals and in the synthesis of polyfunctional molecules.[1-5] In this Chapter, PPh_3-assisted esterification of acyl fluorides with ethers via C(sp^3)−O bond cleavage was introduced. The preparation and degradation of ethers have often been witnessed in an important synthetic strategies for protection/deprotection of hydroxyl groups. Although numerous studies on demethylation in aromatic methyl ethers have been reported,[6-10] demethylation of viable aliphatic surrogates has been relatively less explored. Typically, various reagents have been utilized to convert aliphatic methyl ethers into the corresponding alcohols via demethylation, employing $BF_3{\cdot}Et_2O/(CH_3CO)_2O$,[11] BCl_3,[12] BBr_3,[13] $BF_3{\cdot}Et_2O/EtSH$,[14] Me_3SiI,[15] hydrobromic acid/phase-transfer-catalysts,[16] $BBr_3/NaI/15$-crown-5,[17] $(CH_3)_2BBr$,[18] $AlCl_3/NaI/CH_3CN$,[19] BI_3/N,N-diethylaniline.[20]

On the other hand, since 2005, cyclopentyl methyl ether (CPME)[21,22] has become the common solvent in organic reactions.[23-25] Compared with other conventional ethereal solvents such as Et_2O, THF, DME, 1,4-dioxane, methyl tert-butyl ether (MTBE), and 2-MeTHF, CPME displays many advantages, such as inexpensive, high-boiling point (106 ºC), low polarity, lower miscibility with water (1.1 g/100 g), low tendency to form peroxides, narrow explosion range, and stability under strong acidic and basic conditions. With these characteristics of CPME in mind, utility of CPME as a potential reactant in various organic transformations are attractive. To the best of our knowledge, however, the selective C−O bond cleavage in CPME and the utilization of released methoxy group as a methoxylating agent has been unexplored.[26]

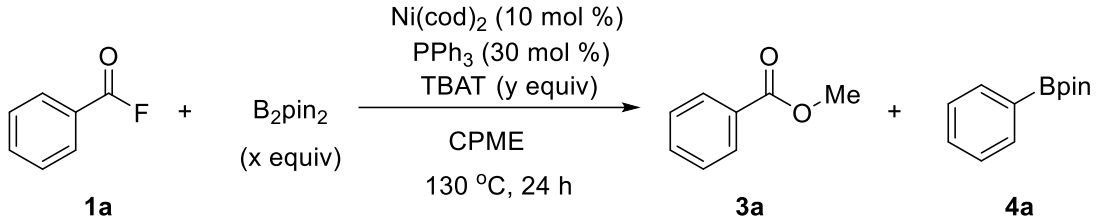
As a part of Author's group ongoing interests in functionalization of acyl halides, in this chapter the Author describe TBAT-mediated nucleophilic methoxylation of acyl fluorides with CPME via both C−OMe and C−F bonds cleavage under transition-metal-free conditions.

4-2. Results and Discussion

4-2-1 TBAT-Mediated Methoxylation of Acyl Fluorides with CPME

During our study on $Ni(cod)_2/PPh_3$-assisted transformations of benzoyl fluoride (**1a**) with organometallic reagents in CPME (**2a**), we serendipitously found 41% of methyl benzoate (**3a**) was formed in the presence of 2.0 equivalent of tetrabutylammonium difluorotriphenylsilicate (TBAT)[27] (Table 4-1, entry 1). Comparation between entry 2, 3 and 4 suggest that diboron is not necessary for **3a** formation.

Table 4-1. Initial Results of Reaction of **1a** with B_2pin_2 in CPME.



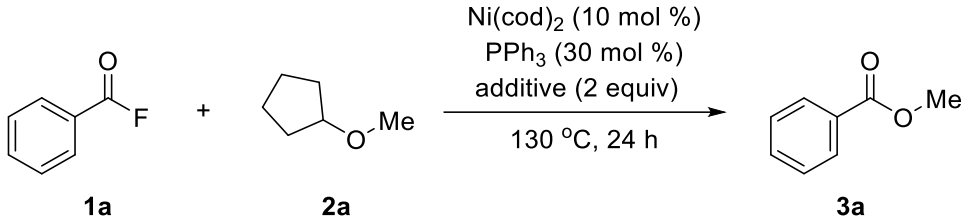
entry[a]	B_2pin_2 (x equiv)	TBAT (y equiv)	yield of **3a** (%)[b]	yield of **4a** (%)
1	2	2	41	20
2	2	0	11	0
3	**0**	**2**	**63**	**0**
4	0	0	20	0

[a]**1a** (0.2 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), B_2pin_2 (0.4 mmol), and TBAT (0.4 mmol) in CPME (**2a**) (1 mL) at 130 ºC for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

Next, various additives were tested, K_3PO_4, K_2CO_3 afforded **3a** less 10% (Table 4-2, entries 1,2). Inferior results were obtained when NaO^{t}Bu, KOH, CsF and TBAF were employed (entries 3-6), it indicated that TBAT is crucial in this transformation. The amount of CPME was screened, 2 to 10 equivalents of CPME in toluene provided 3-13% of **3a** (entries 8-10). When 2.0 mL of CPME was used as both solvent and methoxyl source (entry 12), **3a** was obtained in 71% of GC yield. Several experiments were carried out, which attempt to decreasing the amount of TBAT. To our delight, decreasing the amount of TBAT to 1.5 equivalent the yield was improved to 80% (entry 16). Further increasing or decreasing the loading of TBAT do not have a rise of the yield (entries 14, 15 *vs* 17, 18). The effect of the ligand was elucidated, the yield of **3a** does not change too much when different ligand was employed (entries 19-22). Further screening of the

reaction conditions revealed that cleavage of alkyl C−OMe in CPME proceeded smoothly even in the absence of the nickel catalyst (entry 23). Since the esterification of benzoyl fluorides with CPME could proceed without the nickel catalyzed, the amount of TBAT was evaluated again. Similar tendence was found, 1.0 equivalent of TBAT is important and 30 mol% of PPh_3 could promote the formation of **3a** (entry 30).

Table 4-2. Screening of the Reaction Conditions.



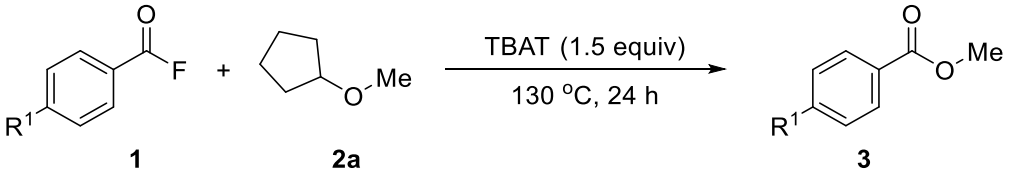
entry[a]	$Ni(cod)_2$ (mol %)	ligand (mol %)	additive (equiv)	**2a** (equiv)	yield of **3a** (%)[b]
1	10	PPh_3 (30)	K_3PO_4 (2 equiv)	43	6
2	10	PPh_3 (30)	K_2CO_3 (2 equiv)	43	3
3	10	PPh_3 (30)	NaO^tBu (2 equiv)	43	25
4	10	PPh_3 (30)	KOH (2 equiv)	43	20
5	10	PPh_3 (30)	CsF (2 equiv)	43	20
6	10	PPh_3 (30)	TBAF (2 equiv)	43	27
7	10	PPh_3 (30)	TBAT (2 equiv)	43	63
8	10	PPh_3 (30)	TBAT (2 equiv)	2	3
9	10	PPh_3 (30)	TBAT (2 equiv)	5	6
10	10	PPh_3 (30)	TBAT (2 equiv)	10	13
11	10	PPh_3 (30)	TBAT (2 equiv)	64	70
12	10	PPh_3 (30)	TBAT (2 equiv)	86	71
13	10	PPh_3 (30)	TBAT (2 equiv)	107	68
14	10	PPh_3 (30)	TBAT (0.5 equiv)	86	64
15	10	PPh_3 (30)	TBAT (1 equiv)	86	70
16	10	PPh_3 (30)	TBAT (1.5 equiv)	86	80
17	10	PPh_3 (30)	TBAT (2.5 equiv)	86	68
18	10	PPh_3 (30)	TBAT (3 equiv)	86	56
19	10	PCy_3 (30)	TBAT (1.5 equiv)	86	76
20	10	PPh_2Py (30)	TBAT (1.5 equiv)	86	71

21	10	DPPE (15)	TBAT (1.5 equiv)	86	77
22	10	Xanthpos (15)	TBAT (1.5 equiv)	86	73
23	-	PPh_3 (30)	TBAT (1.5 equiv)	86	63
24	-	-	-	86	0
25	-	-	TBAT (0.2 equiv)	86	27
26	-	-	TBAT (0.5 equiv)	86	53
27	-	-	TBAT (1 equiv)	86	64
28	-	-	TBAT (2.5 equiv)	86	67
29	-	-	TBAT (5 equiv)	86	67
30	-	PPh_3 (30)	TBAT (1 equiv)	86	74

[a]**1a** (0.2 mmol), $Ni(cod)_2$ (0.02 mmol), ligand, and base (0.4 mmol) in CPME at 130 °C for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

The accelerating effect of PPh_3 was investigated (Table 4-3), **3a** was obtained in 60% GC yield without PPh_3 (entry 1). The yield does not increase even prolong the reaction time to 48 h (entry 2). Performed the reaction with 30 mol% of PPh_3, it provided **3a** in 74% yield (entry 3). Besides, the benzoyl fluoride bearing a phenyl group at *para*-position was also utilized in the control experiment. An accelerating effect of PPh_3 was observed, with 30 mol% of PPh_3

Table 4-3. Effect of PPh_3.



1 **2a** **3**

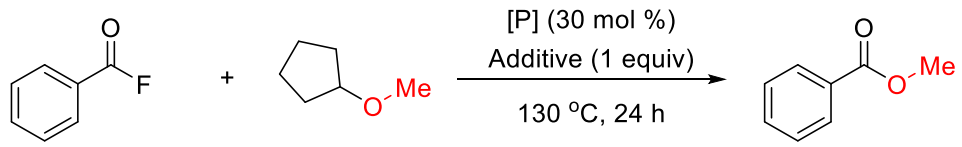
entry[a]	R^1	yield (%)[b]
1	H (**1a**)	60
2[c]	H (**1a**)	61
3[d]	**H (1a)**	**74**
4	Ph (**1b**)	69[e]
5[d]	**Ph (1b)**	**92[e]**

[a]**1a** (0.2 mmol), and TBAT (0.3 mmol) in CPME (2 mL) at 130 °C for 24 h. [b]Determined by GC analysis of the crude mixture, using dodecane as an internal standard. [c]48 h. [d]30 mol % of PPh_3 was

added. [e]NMR yields.

After additional experiments conducted with various reaction parameters, we found that tetrabutylammonium difluorotriphenylsilicate (TBAT)[27] as the additive sufficiently increased the yield of **3a** in 74% yield (Table 4-4, entry 1). PPh_3 show superior result than other mono-dentate phosphine ligands (entries 2-4). Compared to TBAT, several tetrabutylammonium halides such as tetrabutylammonium fluoride, -chloride, -bromide, and -iodide were tested, but they were found to be inferior (entries 5-8). Markedly, tetrabutylammonium trifluoromethanesulfonate (NBu_4OTf) did not work at all (entry 9). In terms of other fluoride sources, poor results were obtained when KF or CsF was employed (entries 10-11). Interestingly, in the presence of 18-crown-6, KF gave 34% of **3a** (entry 12), which might prove the importance of a naked fluoride ion. Notably, no trace of **3a** was detected with fluorotriphenysilane (entry 13) or without TBAT (entry 14), indicating that TBAT uniquely mediated this methoxylation event. Careful control experiments resulted in an unexpected accelerating effect on methoxylation with 30 mol % of PPh_3 (entry 1 *vs* entry 15), suggesting that an addition of PPh_3 can enhance the electrophilicity of **1a**, to some extents.[28] It is noteworthy that the identical reaction with benzoyl chloride afforded the lower yield of **3a** (entry 16), suggesting a unique feature of acyl fluoride.

Table 4-4. Deviation from Standard Conditions.



1a **2a** **3a**

entry[a]	[P]	additive	yield of **3a** (%)
1	PPh_3	TBAT	74 (74)[b]
2	$P(OPh)_3$	TBAT	40
3	PCy_3	TBAT	50
4	P^tBu_3	TBAT	45
5	PPh_3	NBu_4F	46
6	PPh_3	NBu_4Cl	30
7	PPh_3	NBu_4Br	14

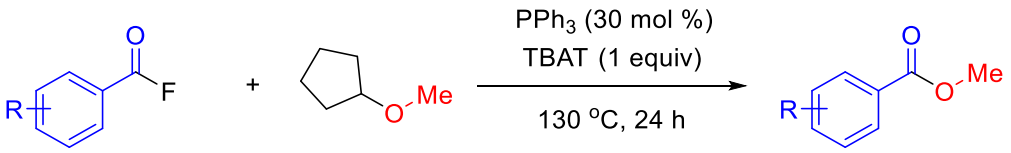
8	PPh_3	NBu_4I	25
9	PPh_3	NBu_4OTf	0
10	PPh_3	KF	12
11	PPh_3	CsF	14
12	PPh_3	18-crown-6/KF	34
13	PPh_3	Ph_3SiF	0
14	PPh_3	-	0
15	-	TBAT	53
16[b]	PPh_3	TBAT	50

[a] Determined by GC analysis of the crude mixture using *n*-dodecane as an internal standard. An isolated yield is given in parentheses. [b] Benzoyl chloride instead of **1a**.

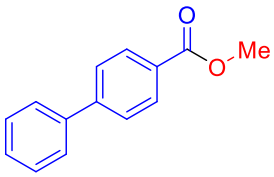
4-2-2 Esterification of Acyl Fluorides with Ethers

With the optimized reaction conditions in hand, we investigated the scope and limitation of the methoxylation of an array of acyl fluorides **1** with CPME. As shown in Table 4-5, this protocol displayed remarkable tolerance towards the substitution pattern and a steric effect. Both electron-donating and sterically encumbering substituents in any positions of the aryl ring gave good results. Another interesting feature of this reaction is that alkyl aryl ethers such as **3c** and **3d** were inert under the conditions. Acyl fluorides bearing electron-donating groups provided the corresponding products **3e**-**3g** in 64-90% isolated yields. When acyl fluorides with electron-withdrawing groups employed, except for 4-nitrobenzoyl fluoride (**1i**), the desired products **3h**, **3j**, and **3k** were obtained in good yields. Particularly, an ester group can also be tolerated, affording the target product **3l** in 75% yield, which is noteworthy because the esters are known to be incompatible with Me_3SiI.[15] Either more steric hindrance (**3n**) or more electronically positive (**3o**) products were successfully formed in this transformation. Polyaromatic products including naphthalenes (**3p**-**3q**) and anthracene (**3r**) motifs also exhibited moderate to good levels of reactivity. Moreover, oxygen- (**3s** and **3t**), sulfur-containing heterocycles (**3u**) did not interfere toward the ester formation. To our delight, the primary and tertiary alkylated acyl fluorides also could accommodate under optimal conditions, afforded corresponding ester **3v** and **3w** in moderate yields.

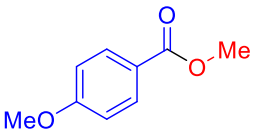
Table 4-5. Methoxylation of Acyl Fluorides with CPME.[a,b]



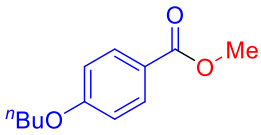
1 **2a** **3**



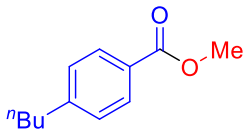
3b, 92%



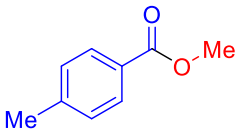
3c, 88%



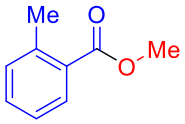
3d, 78%



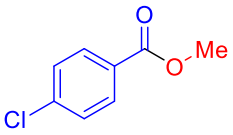
3e, 64%



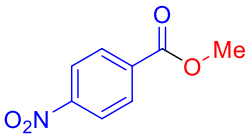
3f, 90%



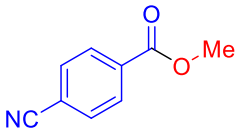
3g, 87%



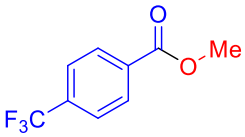
3h, 92%



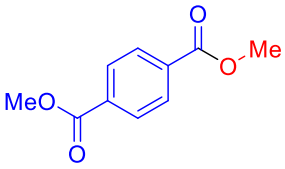
3i, 31%



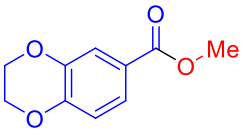
3j, 80%



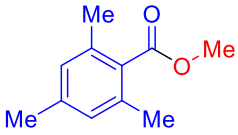
3k, 78%



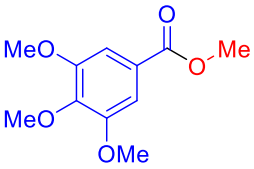
3l, 75%



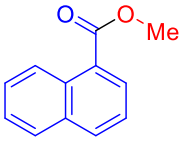
3m, 93%



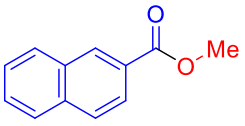
3n, 61%



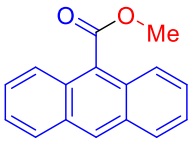
3o, 70%



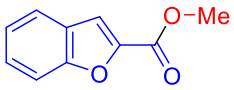
3p, 73%



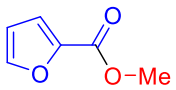
3q, 83%



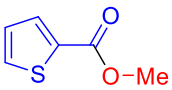
3r, 52%



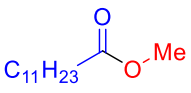
3s, 42%



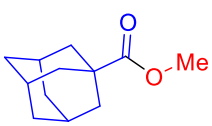
3t, 80%



3u, 70%



3v: 45%

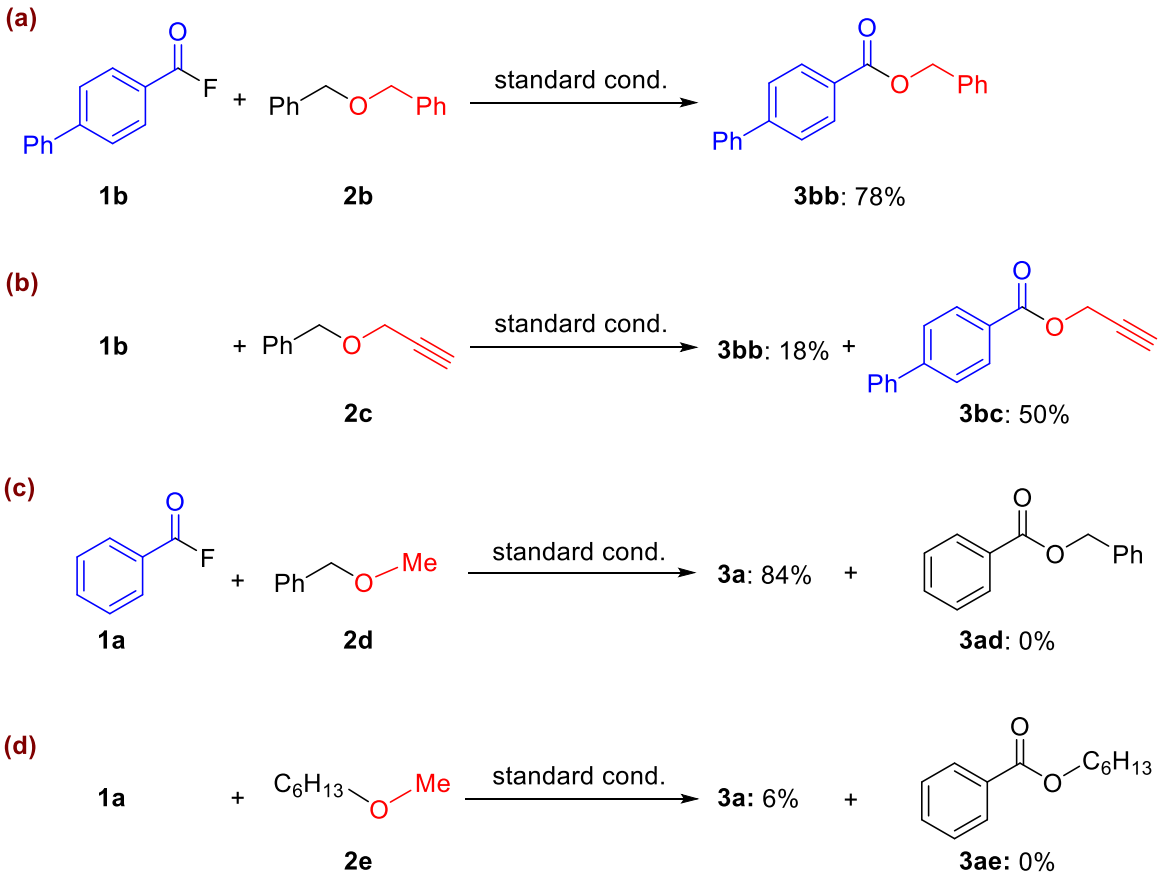


3w: 56%

[a] Reaction conditions: acyl fluorides **1** (0.2 mmol), **2a** (2 mL), PPh_3 (0.06 mmol), TBAT (0.2 mmol), 130 °C, 24 h. [b] Isolated yields.

Given a regiospecific cleavage of C−O bond in CPME, we reasoned that other ethers could also be applied in alkoxylation of acyl fluorides (Scheme 4-1). Dibenzyl ether (**2b**) was also a good substrate, resulting in the formation of **3bb** in 78% yield (Scheme 4-1a). When benzyl propargyl ether (**2c**) was employed, a propargyl group was installed preferentially into the product to afford **3bc** in 50% yield, along with 18% of **3bb** (Scheme 4-1b). Subsequently, unsymmetrical benzyl methyl ether (**2d**) smoothly gave **3a** in 84% yield with a high regiospecificity (Scheme 4-1c). In a sharp contrast, *n*-hexyl methyl ether failed to undergo the reaction, leading to only 6% of **3a** and no competitive product **3ae** was detected (Scheme 4-1d). Although the cleavage patterns highly depend on the reagents added,[1-5] the regiospecific C−O bond cleavage in this transformation can be explained by the stability of the resulting carbocations.

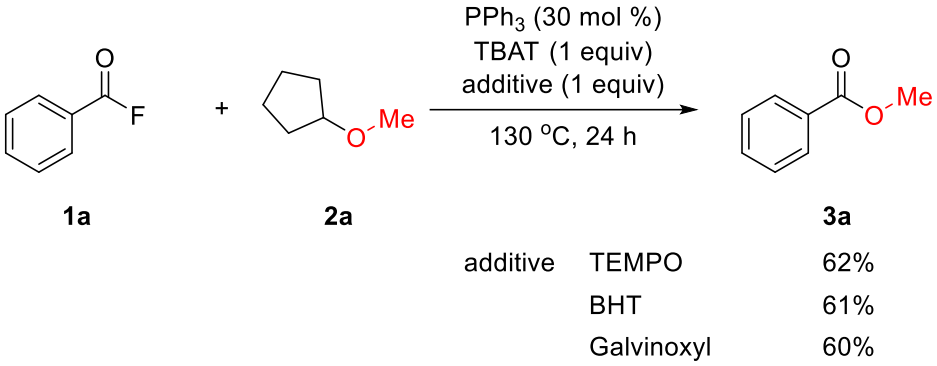
Scheme 4-1. Esterification of Acyl Fluorides with Various Ethers.



4-2-3 Mechanistic Studies

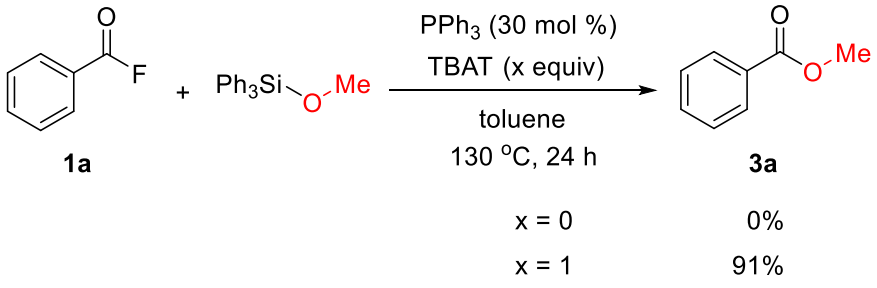
To clarify the reaction mechanism, we performed the methoxylation in the presence of radical scavengers (Scheme 4-2). Consequently, in the presence of equimolar amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), 2,6-di-tert-butyl-4-methylphenol (BHT), or 9,10-dihydroanthracene (DHA), the reaction proceeded with comparable efficiency to that without a radical scavenger, ruling out a radical pathway of this transformation.

Scheme 4-2. Methoxylation in the Presence of Radical Scavengers.



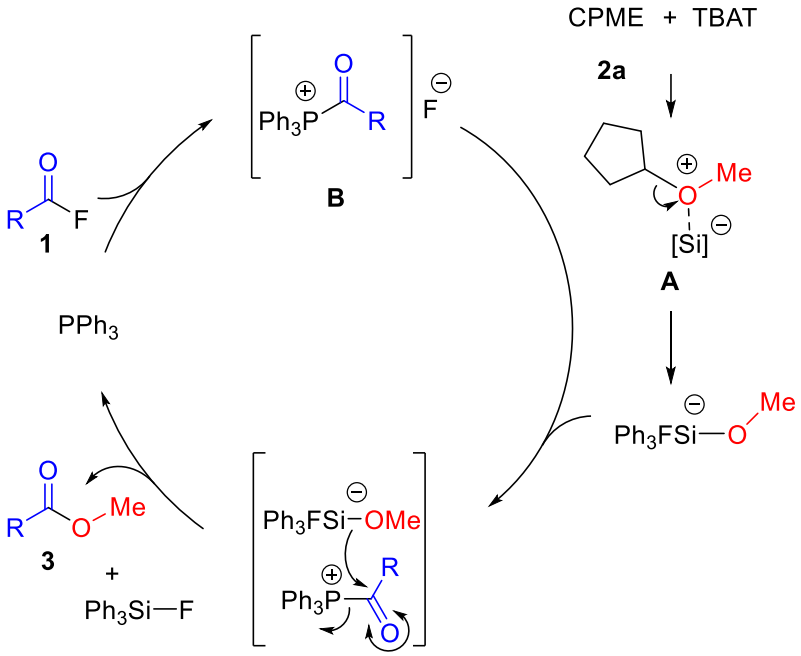
Next, we hypothesized that this transformation might proceed via a silyl methyl ether as the intermediate.[29] When we carried out the reaction using Ph_3SiOMe instead of CPME under the optimized conditions (Scheme 4-3), no desired product **3a** was formed in the absence of TBAT, along with the recovered **1a** (91%) and Ph_3SiOMe (95%). In a sharp contrast, the reaction of **1a** with Ph_3SiOMe in the presence of TBAT, 91% of **3a** was obtained. These results indicated that the reaction of TBAT with CPME generates Ph_3SiOMe via penta- or hexacoordinate silicates.[30] Hypervalent silicates are the key organosilicon species to promote the nucleophilic substitution step, which is normally reluctant with less nucleophilic tetracoordinate organosilicon compounds.[31]

Scheme 4-3. Methoxylation with Ph_3SiOMe.



A plausible reaction mechanism is outlined in Scheme 4-4. Initially, CPME (**2a**) interacts with TBAT to form a hypervalent silicate **A**, which is supposed to cleave C−OMe bond, affording Ph_3SiOMe. Meanwhile, an acyl fluoride **1** react with PPh_3 to generate phosphonium **B** which can be more electrophilic to participate in methoxylation with the formed fluoride-assisted nucleophilic attach of a methoxide anion to a carbonyl group, giving the desired product **3** and Ph_3SiF which was confirmed by $^{19}F\{^1H\}$ NMR spectrum. Although a role of a catalytic amount of PPh_3 has not been clarified, the formation of phosphonium might support a nucleophilic attach of a methoxide to **1**.

Scheme 4-4. Proposed Mechanism.



4-3. Summary

In summary, we report TBAT-mediated methoxylation via the regiospecific cleavage of the inert C−OMe bond. This protocol demonstrated good functional group tolerance under metal-free conditions. Furthermore, chemoselective cleavage of aliphatic ethers, even in the presence of aromatic ethers, are quite difficult by conventional reagents. We believe that our study constitutes an important phenomenon toward a more practical use of readily available aliphatic ethers as coupling partners. Further explorations of related transformations via C−O scission are currently underway in our laboratory.

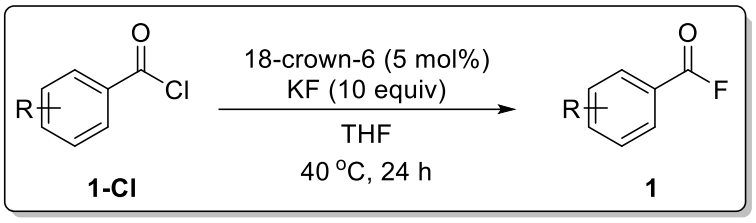
4-4. Experimental Section

4-4-1 General Instrumentation and Chemicals

Unless otherwise noted, all the reactions were carried out under an Ar atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 ºC) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using Silica gel 60 N (spherical, neutral, 40-100 μm) from Kanto Chemicals Co., Ltd. ^{1}H NMR spectra were recorded on Varian INOVA-600 (600 MHz) or Mercury-400 (400 MHz) spectrometers. Chemical shifts (δ) are in parts per million relative to $CDCl_3$ at 7.26 ppm for ^{1}H. The NMR yields were determined using dibromomethane as an internal standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

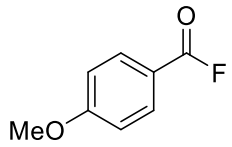
4-4-2 Experimental Procedures

4-4-2-1 Representative Procedure for the Synthesis of Aroyl Fluorides from Acid Chlorides



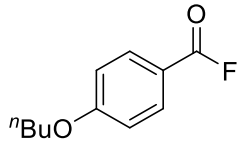
To a 50 mL of Schlenk tube charged with a magnetic stirrer bar, were successively added aroyl chlorides **1-Cl** (4.0 mmol), 18-crown-6 (52.9 mg, 0.2 mmol, 5 mol %), KF (2.32 g, 40 mmol, 10 equiv), and THF (20 mL). After the reaction was stirred at 40 ºC for 24 h, the insoluble inorganic solid (KF or KCl) was filtered, and the volatiles were concentrated using a rotary evaporator. The crude product was purified by bulb-to-bulb distillation to afford the corresponding aroyl fluorides **1**.

4-Methoxybenzoyl fluoride (1c)[32]



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 6.98 (dd, *J* = 9.0 Hz, 1.4 Hz, 2H), 7.96-8.02 (m, 2H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ 15.94.

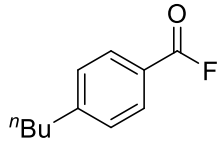
4-Butoxylbenzoyl fluoride (1d)



Yield was 44%. Distillation: 140 ºC/80 mmHg.

^{1}H NMR ($CDCl_3$, 600 MHz, rt): *δ* 0.98 (t, *J* = 7.5 Hz, 3H), 1.50 (sext, *J* = 7.4 Hz, 2H), 1.77-1.82 (m, 2H), 4.04 (t, *J* = 6.6 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 151 MHz, rt) *δ* 13.9, 19.2, 31.1, 68.3, 114.9, 116.6 (d, $^{2}J_{C–F}$ = 62 Hz), 133.8 (d, $^{3}J_{C–F}$ = 5 Hz), 157.4 (d, $^{1}J_{C–F}$ = 339 Hz), 165.0.; $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 564 MHz, rt) *δ* 15.7. FT-IR (neat, cm^{-1}): 2961 (s), 2938 (s), 2873 (m), 1803 (s), 1605 (s), 1510 (s), 1470 (m), 1319 (m), 1254 (s), 1171 (s), 1109 (m), 1024 (s), 999 (s), 968 (m), 846 (s), 691 (m). Anal. Calcd for $C_{11}H_{13}FO_2$: C, 67.33; H, 6.68%. Found: C, 66.96; H, 6.89%.

4-Butylbenzoyl fluoride (1e)

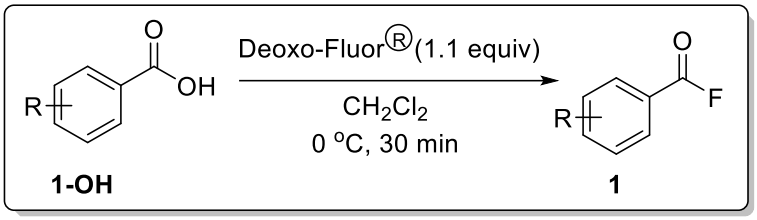


Yield was 30%. Distillation: 140 ºC/80 mmHg.

^{1}H NMR ($CDCl_3$, 600 MHz, rt): *δ* 0.94 (t, *J* = 7.2 Hz, 3H), 1.36 (sext, *J* = 7.6 Hz, 2H), 1.60-1.65 (m, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 151 MHz, rt) *δ* 14.0, 22.4, 33.2, 36.0, 122.4 (d, $^{2}J_{C–F}$ = 60 Hz), 129.3, 131.7 (d, $^{3}J_{C–F}$ = 5 Hz), 151.6, 157.7 (d, $^{1}J_{C–F}$ = 343 Hz); $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 564 MHz, rt) *δ* 17.4. FT-IR (neat, cm^{-1}): 2959 (s), 2932 (s), 2866 (m), 1807 (s), 1773 (m), 1609 (s), 1462 (w), 1418 (w), 1256 (s), 1177 (m),

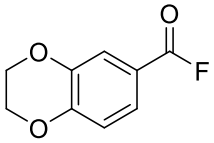
1107 (m), 1007 (s), 878 (m), 845 (m), 737 (m), 694 (w). Anal. Calcd for $C_{11}H_{13}FO$: C, 73.31; H, 7.27%. Found: C, 73.29; H, 7.41%.

4-4-2-2 Representative Procedure for the Synthesis of Aroyl Fluorides from Carboxylic Acids[33]



To a 20 mL of Schlenk tube charged with a magnetic stirrer bar, were successively added carboxylic acids **1-OH** (3.0 mmol) and CH_2Cl_2 (15 mL). After the mixture was stirred at 0 ºC, Deoxo-Fluor® reagent (1.1 equiv, 608 μL, 3.3 mmol) was slowly added to the reaction mixture. After the reaction mixture was stirred at 0 ºC for 30 min, the solution was slowly poured into saturated $NaHCO_3$, and after CO_2 evolution ceased it was extracted into CH_2Cl_2 (3 × 15 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography (Hexane:Et_2O = 10:1) to afford the corresponding aroyl fluorides **1**.

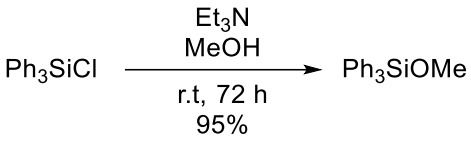
2,3-Dihydrobenzo[b][1,4]dioxine-6-carbonyl fluoride (1m)



Yield was 89%. Melting point: 88-89 °C.

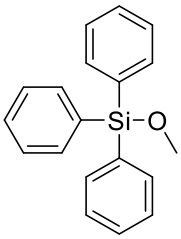
^{1}H NMR ($CDCl_3$, 600 MHz, rt): δ 4.29-4.30 (m, 2H), 4.34-4.36 (m, 2H), 6.95 (dd, J = 8.4, 1.2 Hz, 1H), 7.55-7.57 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz, rt) δ 64.1, 64.9, 117.7 (d, $^2J_{C-F}$ = 62 Hz), 118.0, 120.9 (d, $^3J_{C-F}$ = 5 Hz), 125.7 (d, $^3J_{C-F}$ = 3 Hz), 143.8, 150.0, 157.2 (d, $^1J_{C-F}$ = 340 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 564 MHz, rt) δ 16.5. FT-IR (neat, cm^{-1}): 1792 (s), 1609 (m), 1585 (m), 1506 (m), 1456 (m), 1436 (m), 1336 (m), 1304 (s), 1180 (m), 1123 (m), 1064 (m), 1040 (s), 1005 (m), 895 (s), 878 (m), 826 (w), 748 (s), 716 (m), 660 (w). Anal. Calcd for $C_9H_7FO_3$: C, 59.35; H, 3.87%. Found: C, 59.38; H, 3.71%.

4-4-2-3 Synthesis of Methoxytriphenylsilane



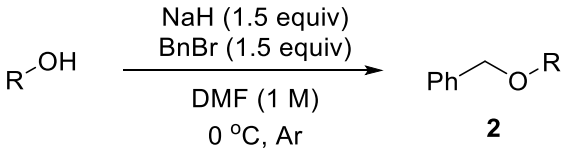
To methanol (2 mL) were added chlorotriphenylsilane (4 mmol) and triethylamine (6 mmol). The reaction mixture was stirred under Ar for 72 h until full conversion. Next, the reaction mixture was evaporated to dryness, dissolved in diethyl ether (100 mL), and washed with H_2O (1 × 5 mL, 2 × 2.5 mL). Organic phase was dried over sodium sulfate and evaporated. The crude product was purified by flash chromatography (Hexane:EtOAc = 40:1) to afford the methoxytriphenylsilane in 95% yield.

Methoxytriphenylsilane[34]



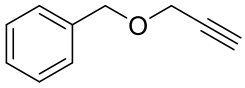
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 7.37-7.47 (m, 9H), 7.60-7.67 (m, 6H).

4-4-2-4 General Methods for Synthesis of Ether Derivatives



To a solution of alcohol (20 mmol) in DMF (20 mL) was added sodium hydride (1.2 g, 30 mmol, 60% in paraffin oil) at 0 ºC under argon. After stirring for 30 min, benzyl bromide (2.95 mL, 30 mmol) was added to the reaction mixture at 0 ºC under argon and the solution was warmed to room temperature. After further stirring for 5 h, the reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (20 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 40:1) to give the corresponding benzyl ether derivative **2**.

((Prop-2-yn-1-yloxy)methyl)benzene (2c)[35]



Propargylic alcohol (1.16 mL, 20 mmol) was used as a substrate and **2d** (2.34 g, 16 mmol) was obtained in 80% yield after purification by silica-gel column chromatography (hex:EtOAc = 40:1).

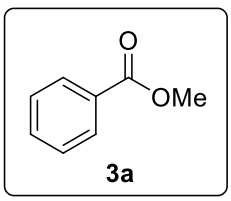
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.47 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 4.62 (s, 2H), 7.29-7.33 (m, 1H), 7.34-7.39 (m, 4H).

4-4-2-5 Esterification Reaction

Representative Procedure for the Esterification of Aroyl Fluorides with Cyclopentyl Methyl Ether

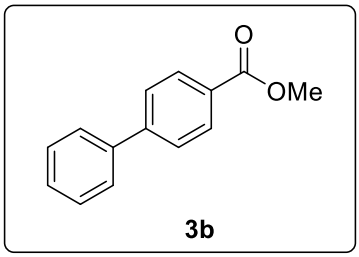
To a 20 mL Schlenk tube were added PPh_3 (30 mol %, 15.7 mg, 0.06 mmol), TBAT (1 equiv., 108 mg, 0.2 mmol), [1,1'-biphenyl]-4-carbonyl fluoride (40.0 mg, 0.2 mmol,) and CPME (2.0 mL). Subsequently, the resulting mixture was heated at 130 ºC. After 24 h, cyclopentyl methyl ether was removed by rotary evaporators (for the high boiling point ether was removed by bulb-to-bulb distillation), the residue was purified by column chromatography (hexane:EtOAc = 20:1) to afford methyl [1,1'-biphenyl]-4-carboxylate (**3b**) (39 mg, 0.184 mmol) in 92% yield. Spectroscopic data for esters match those previously reported in the literature.

Methyl benzoate (3a)[36]



Yield: 74% (20.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.42-7.47 (m, 2H), 7.53-7.58 (m, 1H), 8.02-8.07 (m, 2H).

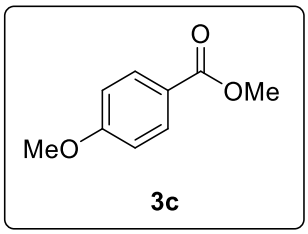
Methyl [1,1'-biphenyl]-4-carboxylate (3b)[37]



3b

Yield: 92% (39.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.61-7.68 (m, 4H), 8.11 (d, *J* = 8.2 Hz, 2H).

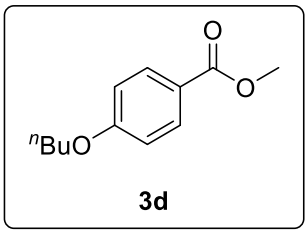
Methyl 4-methoxybenzoate (3c)[36]



3c

Yield: 88% (29.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.88 (s, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H).

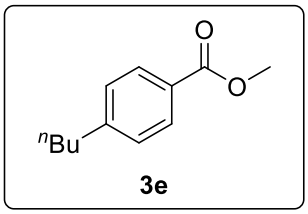
Methyl 4-butoxybenzoate (3d)[38]



3d

Yield: 78% (32.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.46-1.53 (m, 2H), 1.78 (ddt, *J* = 9.1, 7.7, 6.5 Hz, 2H), 3.88 (s, 3H), 4.01 (s, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.92-8.03 (m, 2H).

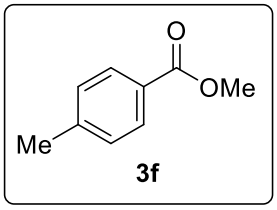
Methyl 4-butylbenzoate (3e)[39]



3e

Yield: 64% (24.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.31-1.40 (m, 2H), 1.55-1.67 (m, 2H), 2.63-2.68 (m, 2H), 3.90 (s, 3H), 7.24 (dt, *J* = 8.6, 0.6 Hz, 2H), 7.90-7.98 (m, 2H).

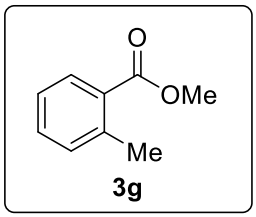
Methyl 4-methylbenzoate (3f)[36]



3f

Yield: 90% (27.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.90 (s, 3H), 7.24 (dt, *J* = 8.0, 0.6 Hz, 2H), 7.89-7.97 (m, 2H).

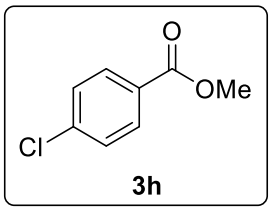
methyl 2-methylbenzoate (3g)[40]



3g

Yield: 87% (26.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.89 (s, 3H), 7.22-7.26 (m, 2H), 7.39 (td, *J* = 7.5, 1.3 Hz, 1H), 7.91 (dd, *J* = 8.2, 1.2 Hz, 1H).

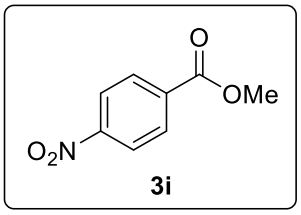
Methyl 4-chlorobenzoate (3h)[36]



3h

Yield: 92% (31.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.95-8.00 (m, 2H).

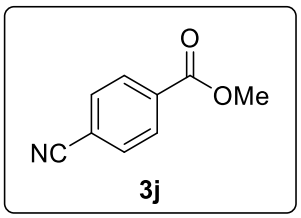
Methyl 4-nitrobenzoate (3i)[41]



3i

Yield: 31% (11.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 8.19-8.23 (m, 2H), 8.26-8.31 (m, 2H).

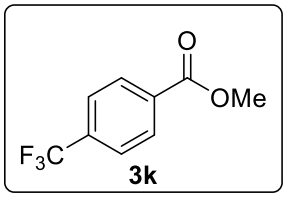
Methyl 4-cyanobenzoate (3j)[42]



3j

Yield: 80% (25.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.71-7.77 (m, 2H), 8.10-8.17 (m, 2H).

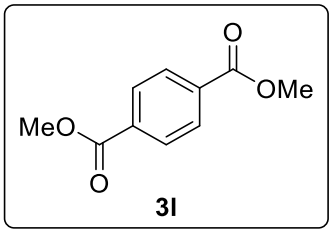
Methyl 4-(trifluoromethyl)benzoate (3k)[36]



3k

Yield: 78% (32.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.69-7.73 (m, 2H), 8.11-8.18 (m, 2H).

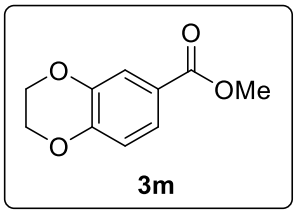
Dimethyl terephthalate (3l)[41]



3l

Yield: 75% (29.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 6H), 8.10 (s, 4H).

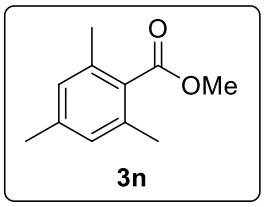
Methyl 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate (3m)[43]



Yield: 93% (36.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.25-4.28 (m, 2H), 4.29-4.32 (m, 2H), 6.86-6.90 (m, 1H), 7.52-7.58 (m, 2H).

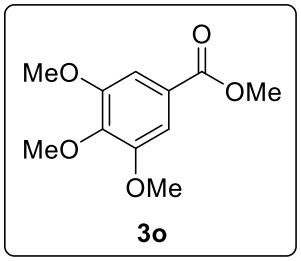
$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 51.94, 64.06, 64.60, 117.08, 118.98, 123.39, 143.12, 147.72, 166.60.

Methyl 2,4,6-trimethylbenzoate (3n)[44]



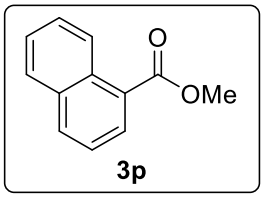
Yield: 61% (21.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 9H), 3.89 (s, 3H), 6.85 (s, 2H).

Methyl 3,4,5-trimethoxybenzoate (3o)[45]



Yield: 70% (31.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (d, *J* = 1.0 Hz, 12H), 7.29 (s, 2H).

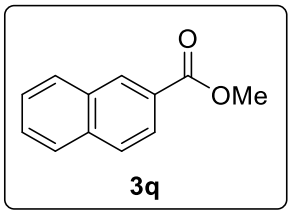
Methyl 1-naphthoate (3p)[40]



Yield: 73% (27.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.48-7.56 (m, 2H),

7.62 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 7.89 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1H), 8.02 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1H), 8.19 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.89-8.95 (m, 1H).

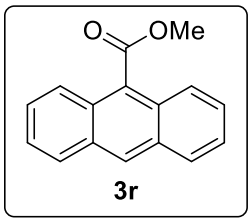
Methyl 2-naphthoate (3q)[46]



3q

Yield: 83% (31.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.57 (dddd, *J* = 19.6, 8.1, 6.9, 1.4 Hz, 2H), 7.88 (dt, *J* = 8.0, 1.2 Hz, 2H), 7.95 (ddt, *J* = 8.0, 1.4, 0.7 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.62 (dd, *J* = 1.6, 0.8 Hz, 1H).

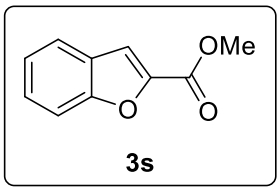
Methyl anthracene-9-carboxylate (3r)[40]



3r

Yield: 52% (24.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 3H), 7.47-7.57 (m, 4H), 8.03 (dd, *J* = 8.4, 4.1 Hz, 4H), 8.54 (s, 1H).

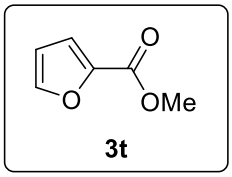
Methyl benzofuran-2-carboxylate (3s)[47]



3s

Yield: 42% (14.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.31 (ddd, *J* = 7.9, 7.2, 0.8 Hz, 1H), 7.46 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.54 (t, *J* = 0.7 Hz, 1H), 7.59 (dq, *J* = 8.3, 0.8 Hz, 1H), 7.69 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H).

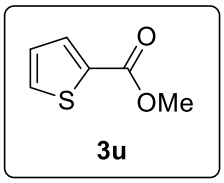
Methyl furan-2-carboxylate (3t)[48]



3t

Yield: 80% (20.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.47 (dd, *J* = 3.5, 1.8 Hz, 1H), 7.14 (dd, *J* = 3.5, 0.9 Hz, 1H), 7.54 (dd, *J* = 1.7, 0.9 Hz, 1H).

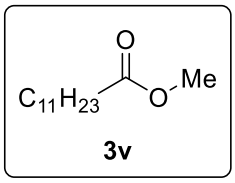
Methyl thiophene-2-carboxylate (3u)[40]



3u

Yield: 70% (20 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.55 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.80 (dd, *J* = 3.7, 1.3 Hz, 1H).

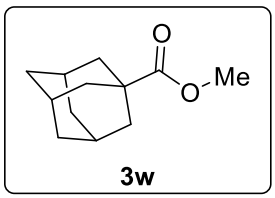
Methyl dodecanoate (3v)[49]



3v

Yield: 45% (19.4 mg); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.90 (m, 3H), 1.23-1.30 (m, 16H), 1.62 (td, J = 7.1, 3.0 Hz, 2H), 2.27-2.32 (m, 2H), 3.66 (s, 3H).

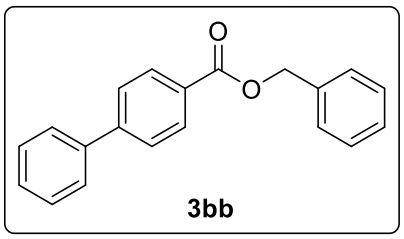
Methyl (3r,5r,7r)-adamantane-1-carboxylate (3w)[50]



3w

Yield: 56% (21.8 mg); white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.68-1.73 (m, 6H), 1.88-1.89 (m, 6H), 1.99-2.02 (m, 3H), 3.64 (s, 3H).

Benzyl [1,1'-biphenyl]-4-carboxylate (3bb)[51]

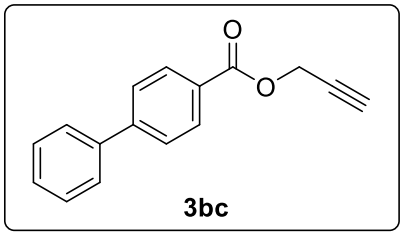


3bb

Yield: 78% (45.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.40 (s, 2H), 7.33-7.43 (m, 4H), 7.45-7.49 (m, 4H), 7.61-7.64 (m, 2H), 7.65-7.68 (m, 2H), 8.13-8.17 (m, 2H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 66.85, 127.20, 127.42, 128.29, 128.31, 128.39, 128.75, 128.98, 129.06, 130.37, 136.22, 140.12, 145.91, 166.47.

Prop-2-yn-1-yl [1,1'-biphenyl]-4-carboxylate (3bc)[52]

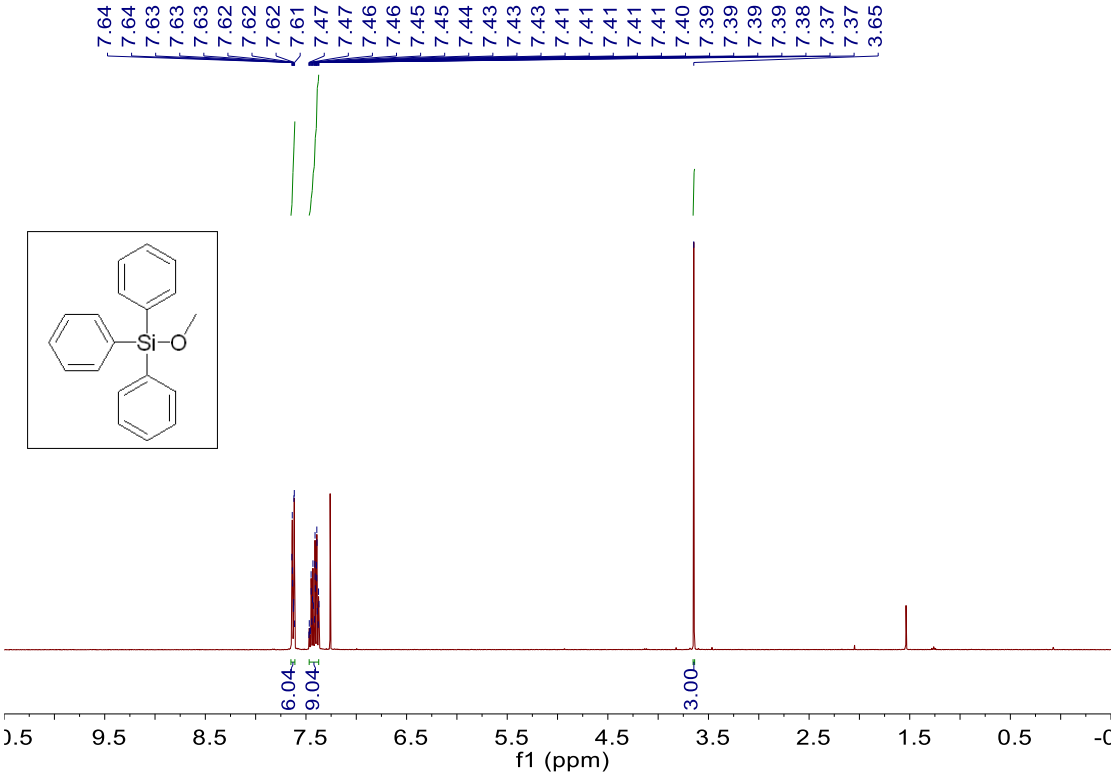


3bc

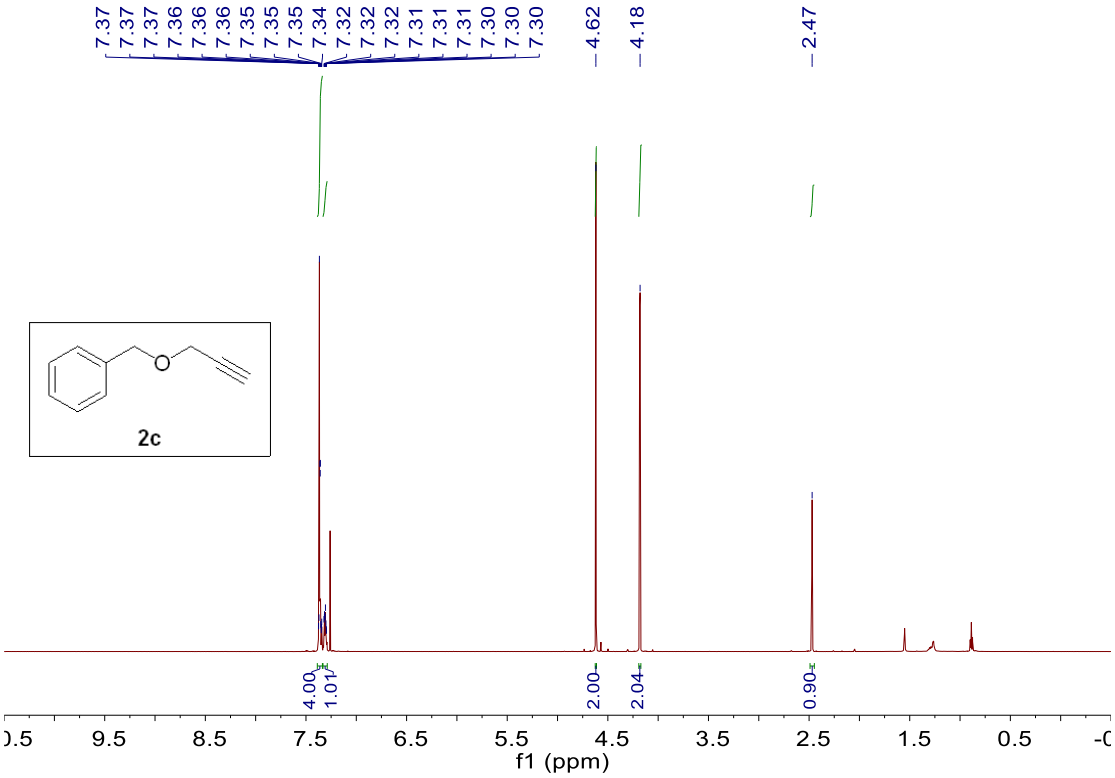
Yield: 50% (23.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.54 (t, J = 2.4 Hz, 1H), 4.96 (d, J = 2.5 Hz, 2H), 7.39-7.43 (m, 1H), 7.45-7.50 (m, 2H), 7.61-7.64 (m, 2H), 7.66-7.70 (m, 2H), 8.12-8.18 (m, 2H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 52.46, 75.02, 77.77, 127.10, 127.28, 128.09, 128.23, 128.94, 130.33, 139.86, 146.06, 165.67.

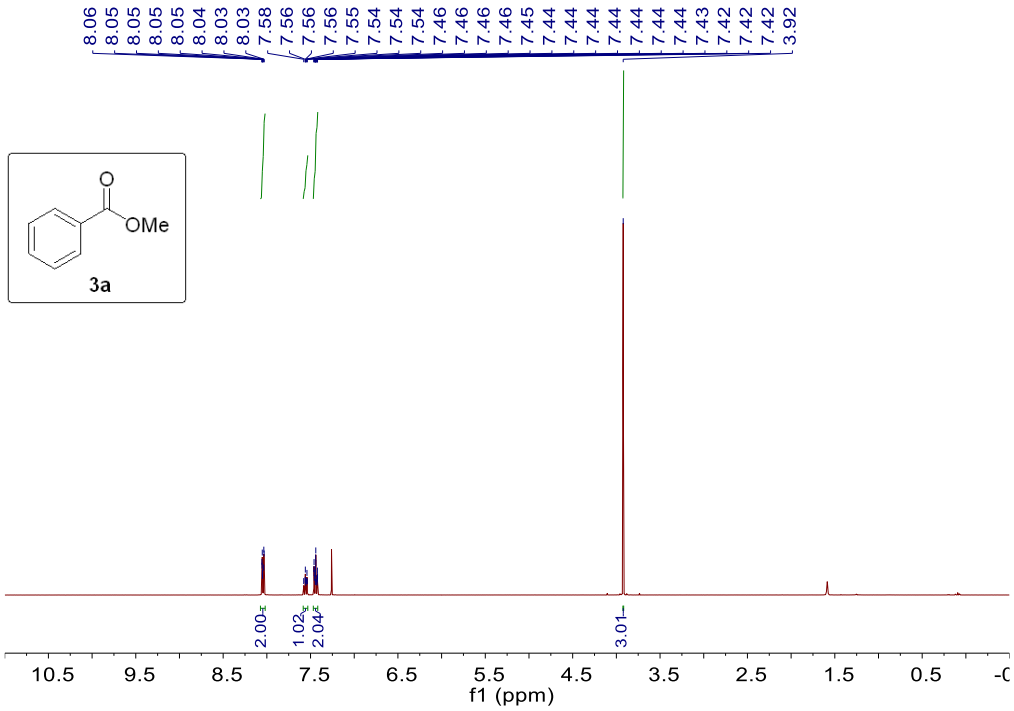
4-4-3 Copies of ^{1}H Charts



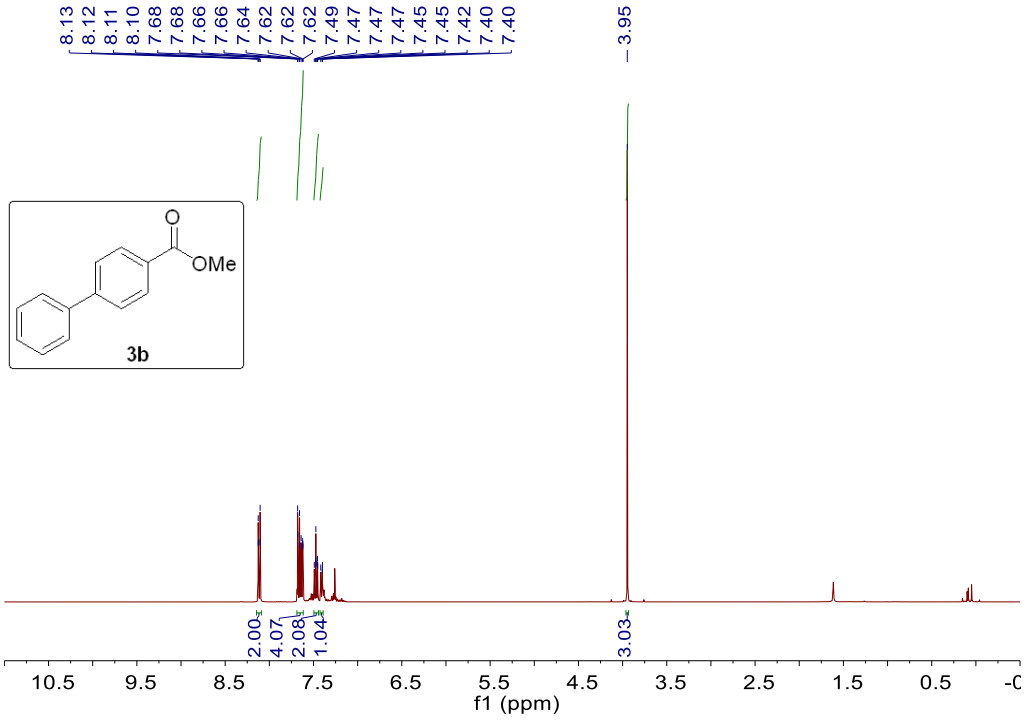
^{1}H NMR (400 MHz) spectrum of methoxytriphenylsilane ($CDCl_3$, rt).



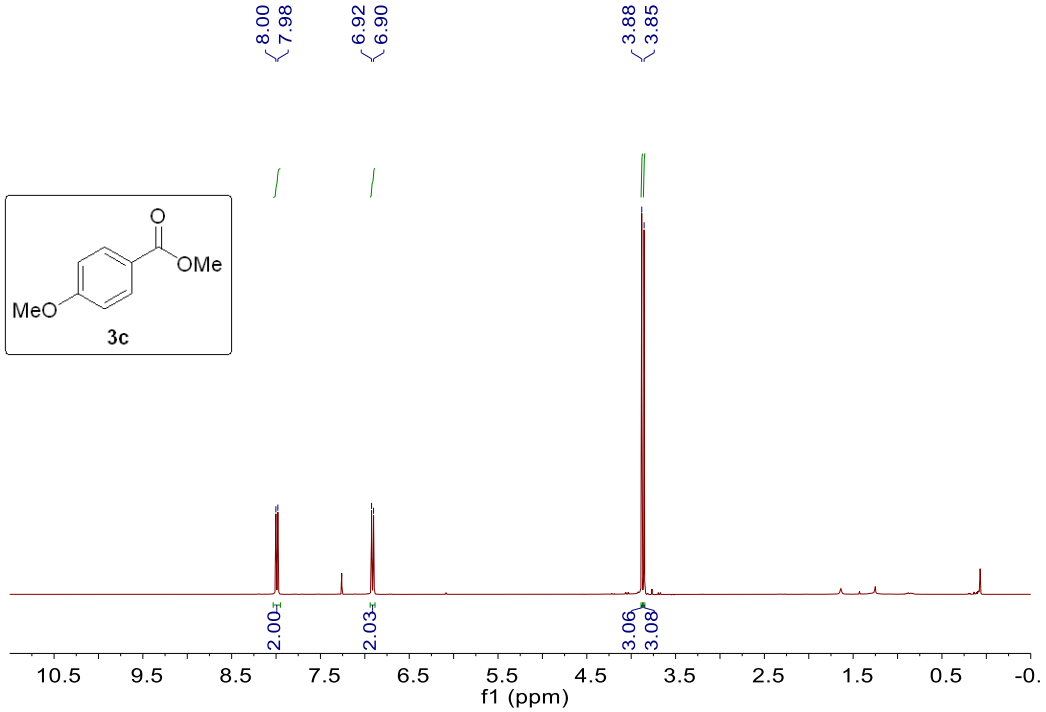
^{1}H NMR (600 MHz) spectrum of **2c** ($CDCl_3$, rt).



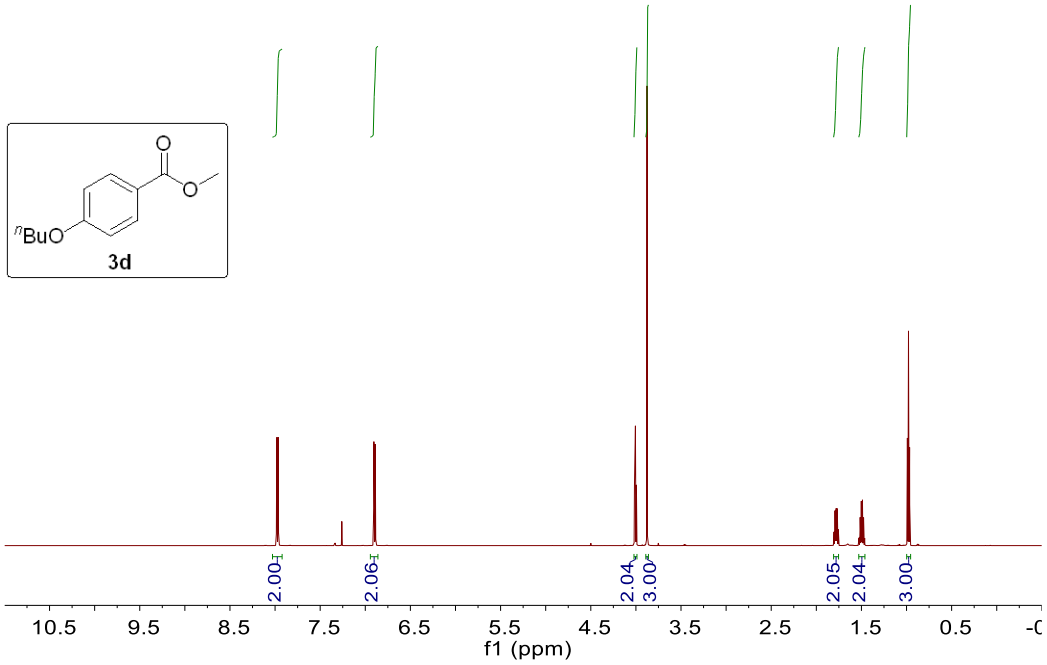
^{1}H NMR (400 MHz) spectrum of **3a** ($CDCl_3$, rt).



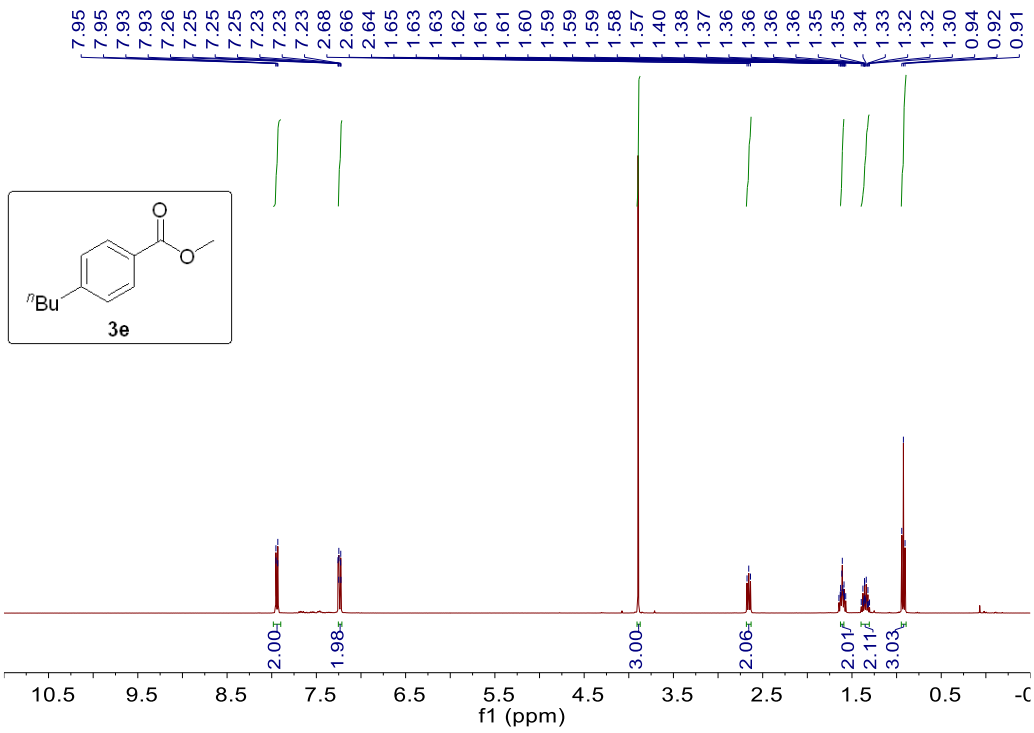
^{1}H NMR (400 MHz) spectrum of **3b** ($CDCl_3$, rt).



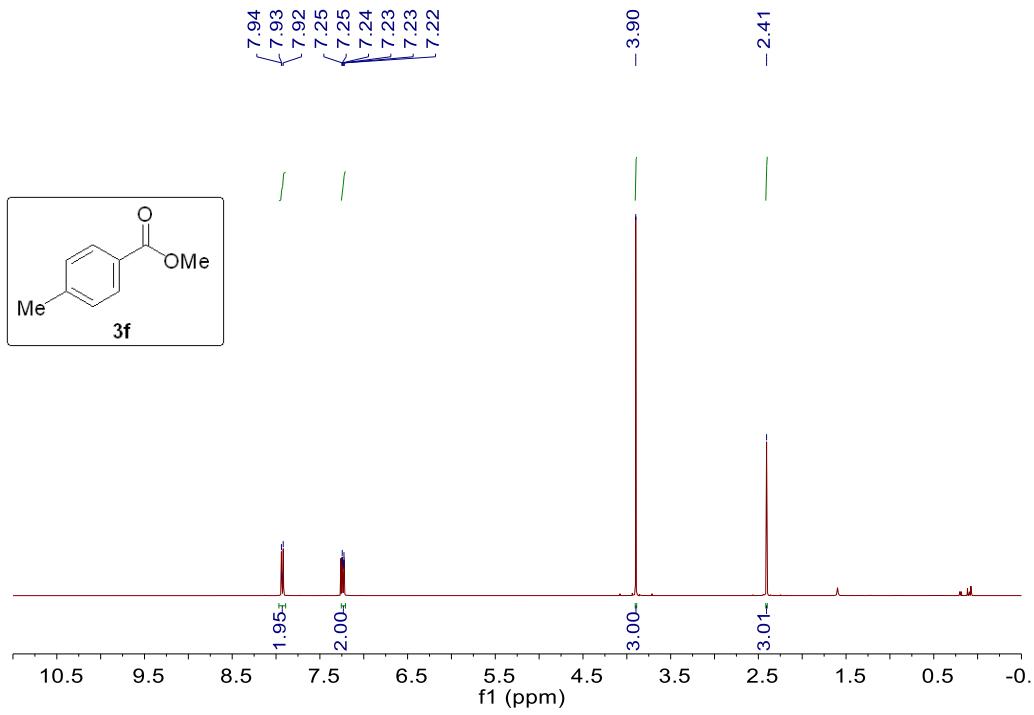
^{1}H NMR (400 MHz) spectrum of **3c** ($CDCl_3$, rt).



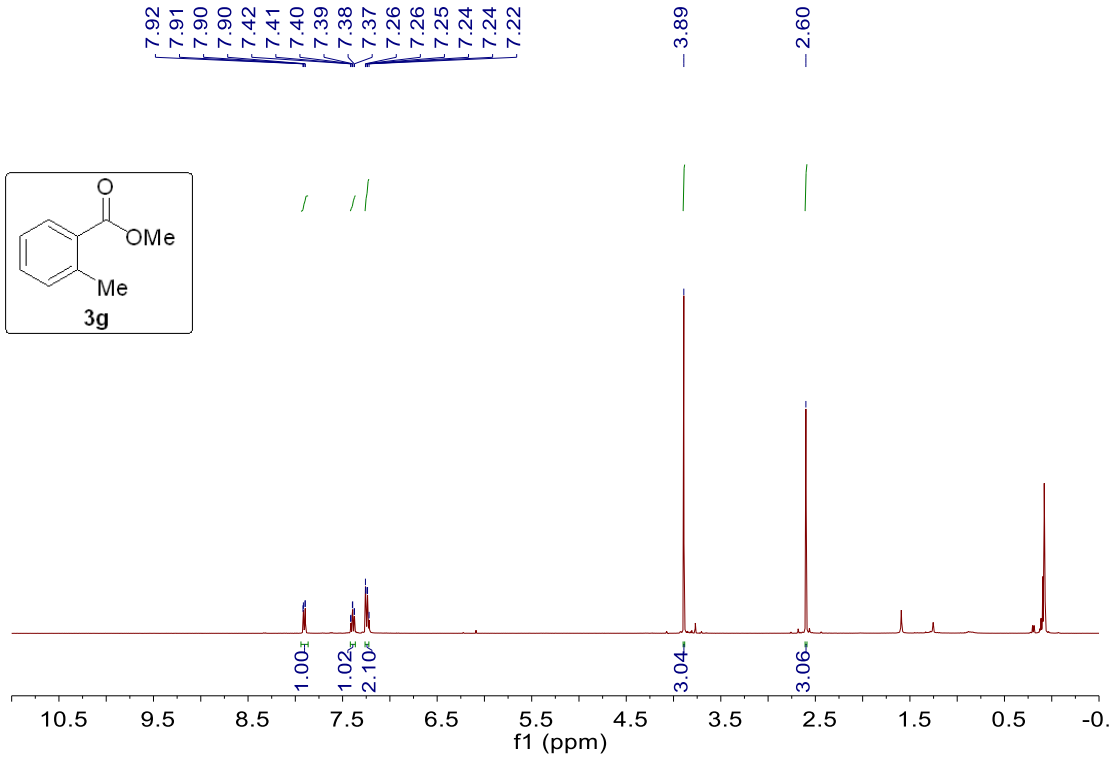
^{1}H NMR (600 MHz) spectrum of **3d** ($CDCl_3$, rt).



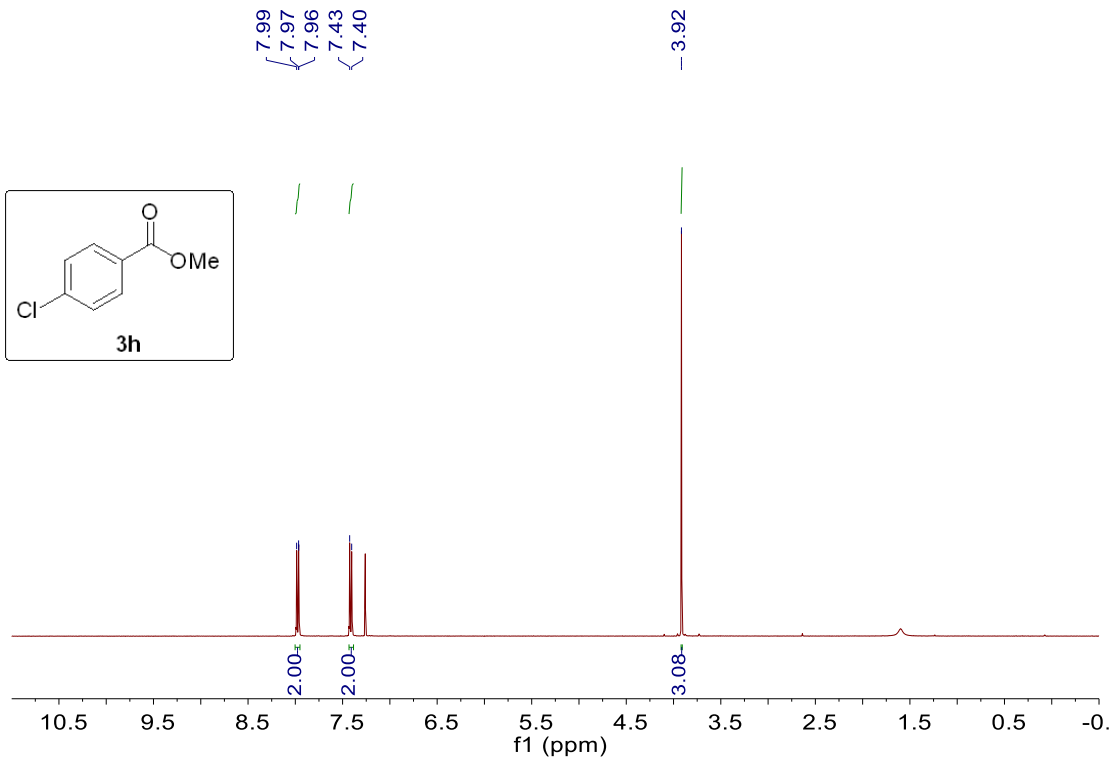
^{1}H NMR (400 MHz) spectrum of **3e** ($CDCl_3$, rt).



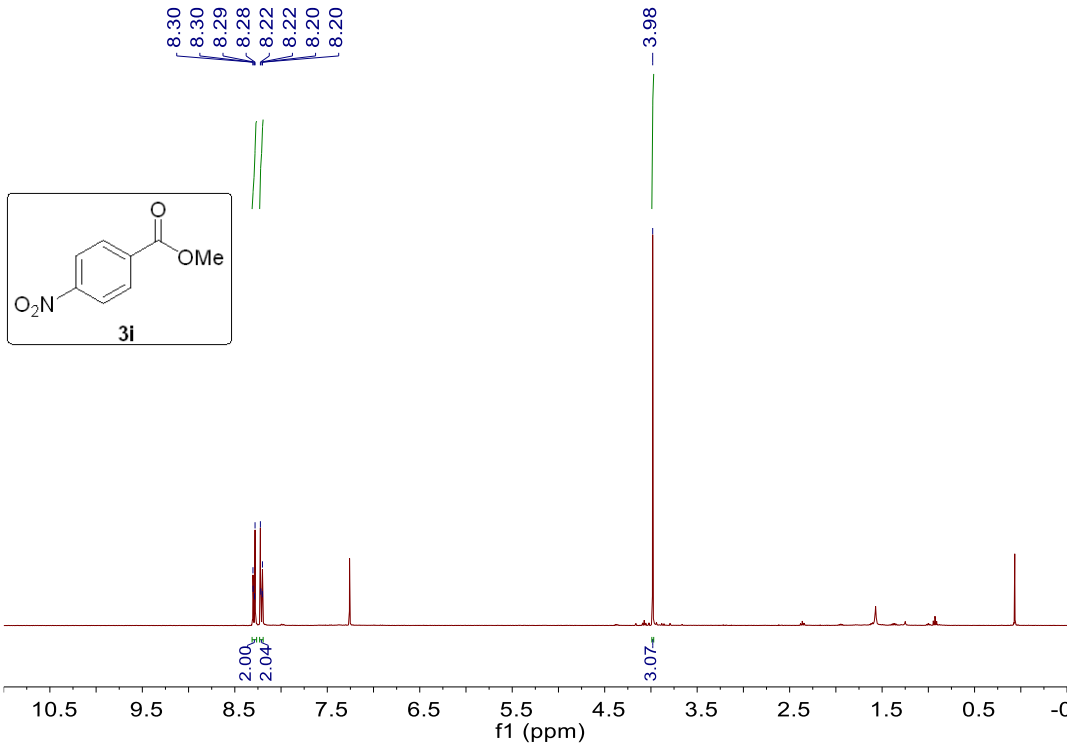
^{1}H NMR (400 MHz) spectrum of **3f** ($CDCl_3$, rt).



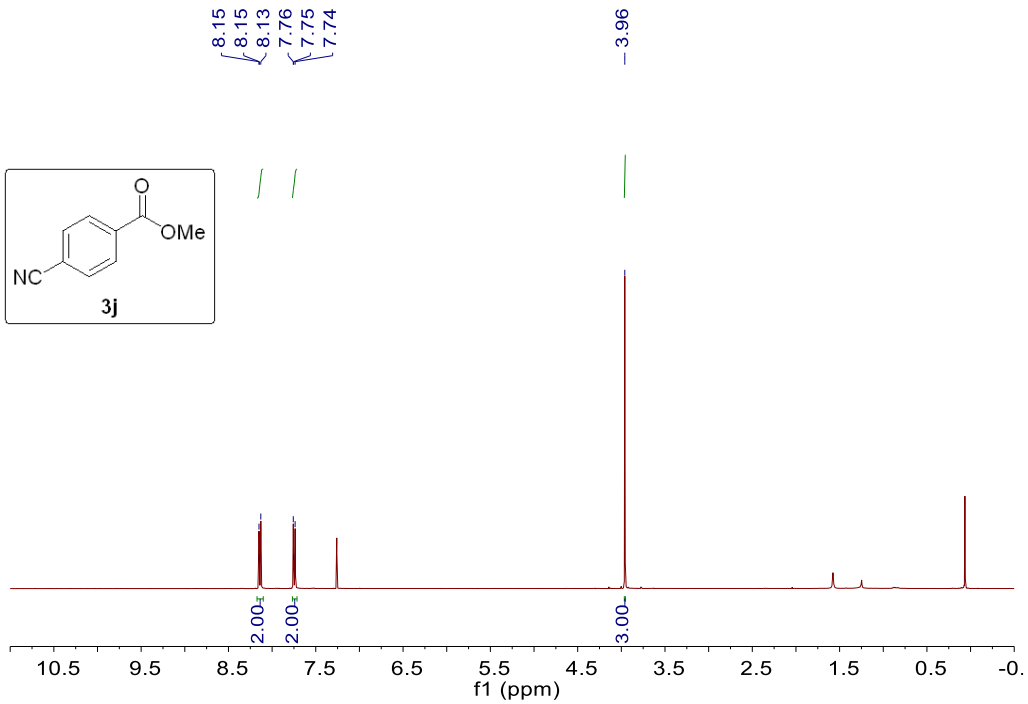
^{1}H NMR (400 MHz) spectrum of **3g** ($CDCl_3$, rt).



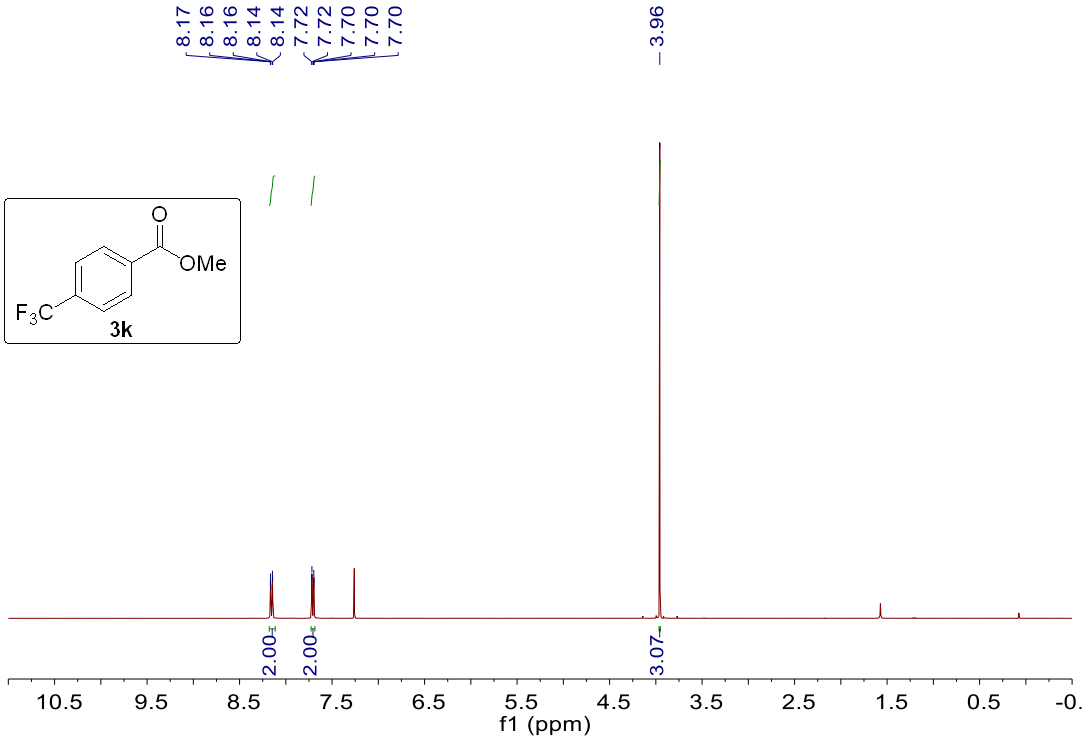
^{1}H NMR (400 MHz) spectrum of **3h** ($CDCl_3$, rt).



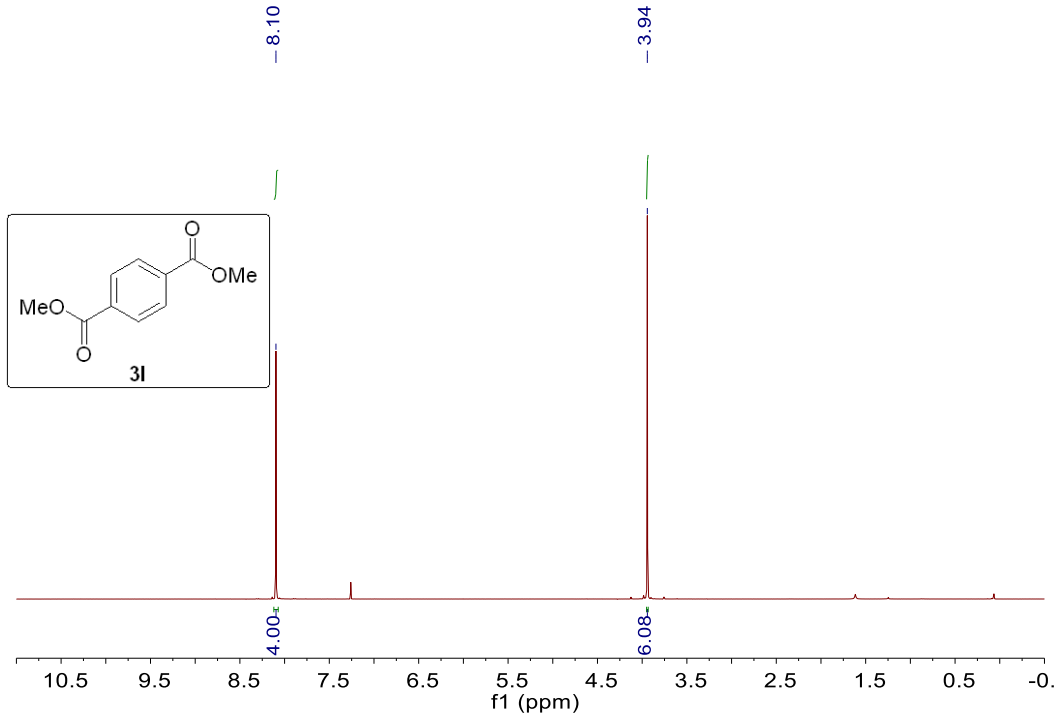
^{1}H NMR (400 MHz) spectrum of **3i** ($CDCl_3$, rt).



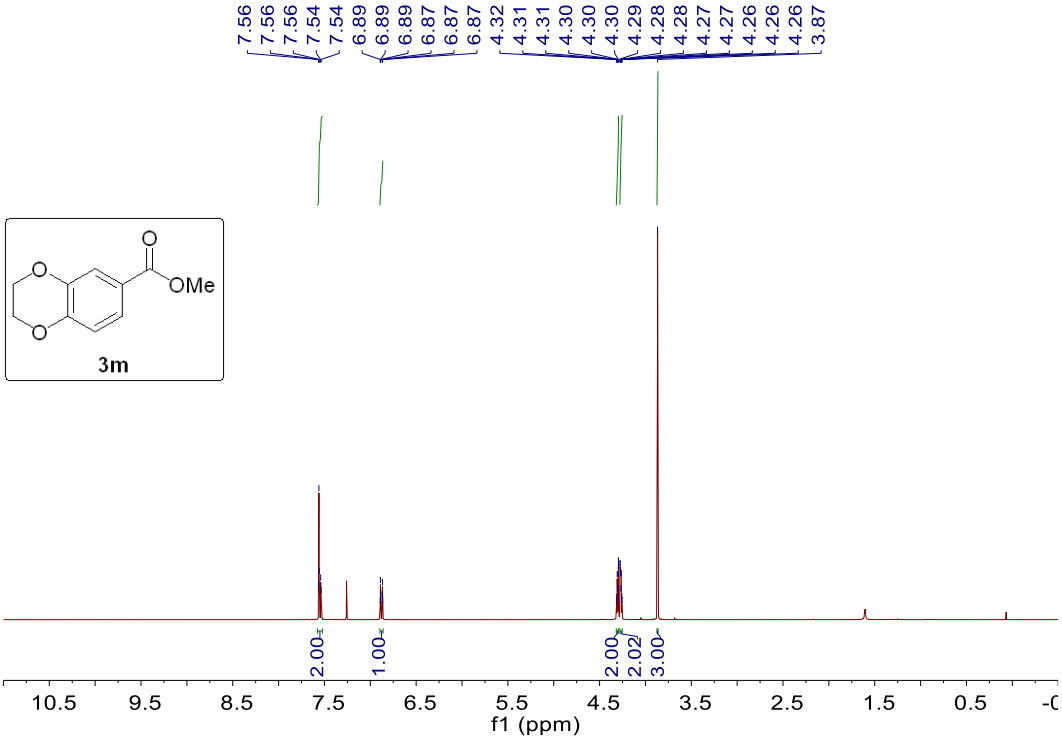
^{1}H NMR (400 MHz) spectrum of **3j** ($CDCl_3$, rt).



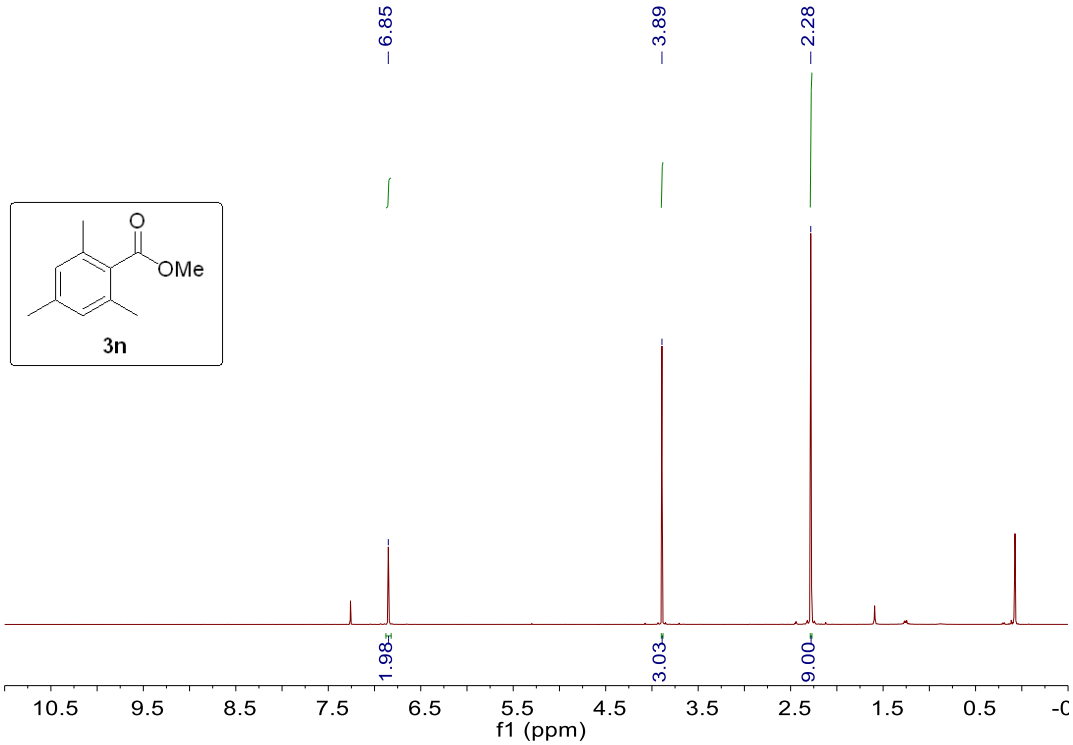
^{1}H NMR (400 MHz) spectrum of **3k** ($CDCl_3$, rt).



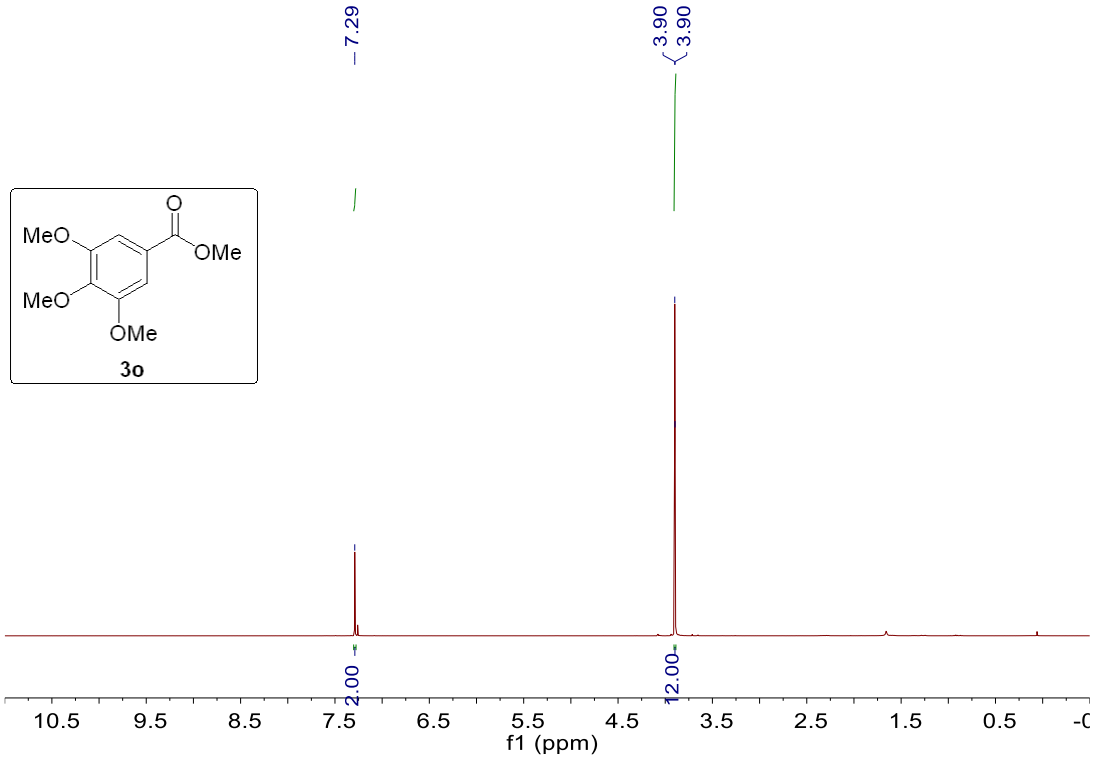
^{1}H NMR (400 MHz) spectrum of **3l** ($CDCl_3$, rt).



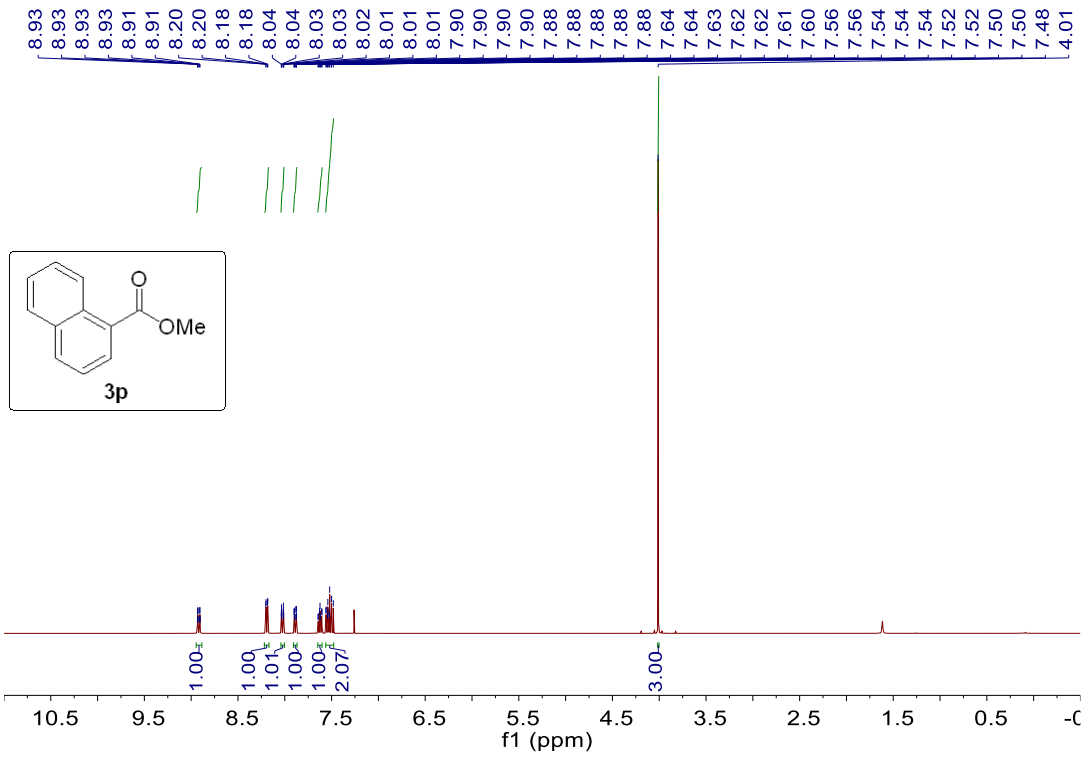
^{1}H NMR (400 MHz) spectrum of **3m** ($CDCl_3$, rt).



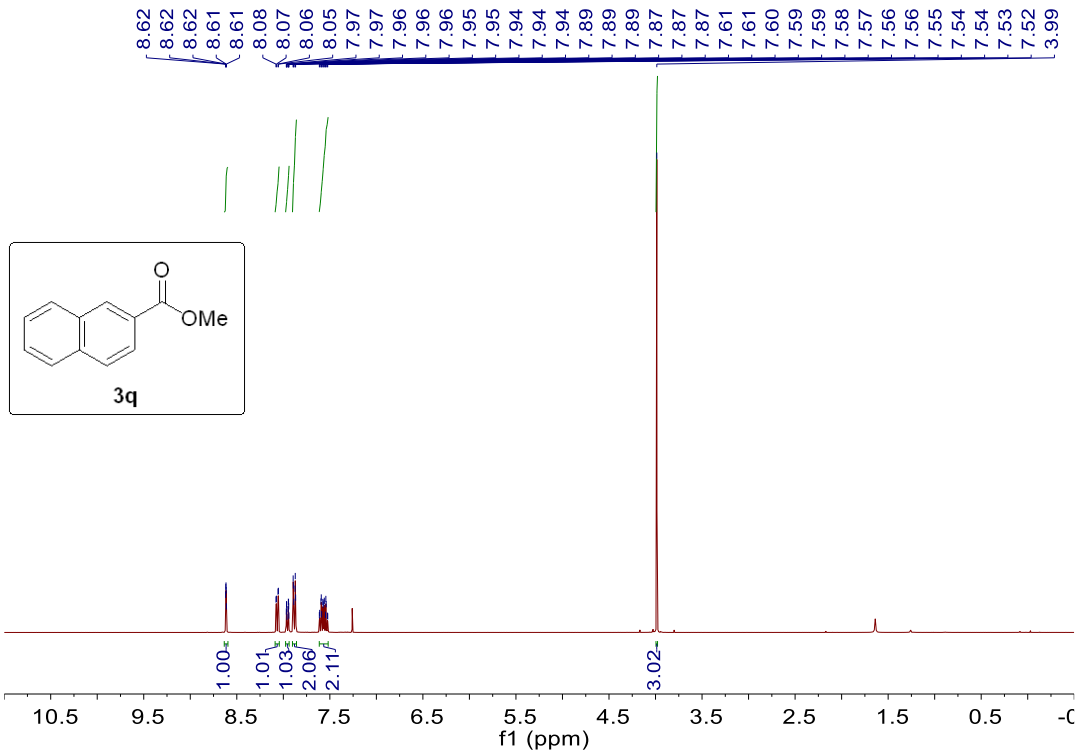
^{1}H NMR (400 MHz) spectrum of **3n** ($CDCl_3$, rt).



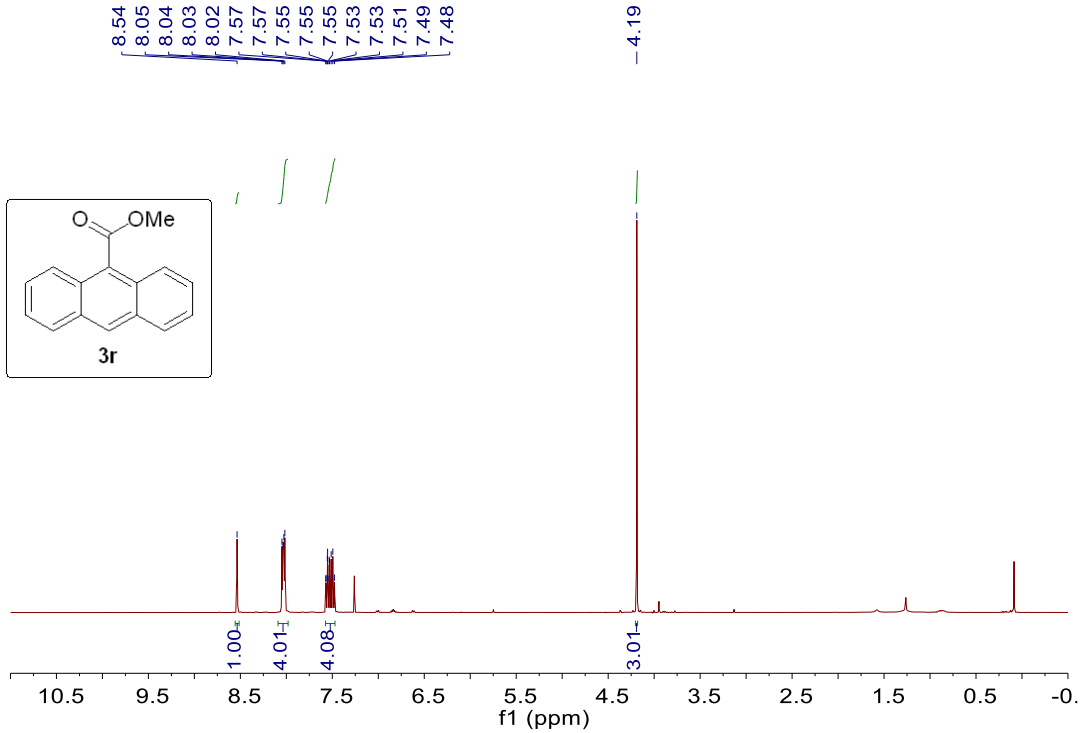
^{1}H NMR (400 MHz) spectrum of **3o** ($CDCl_3$, rt).



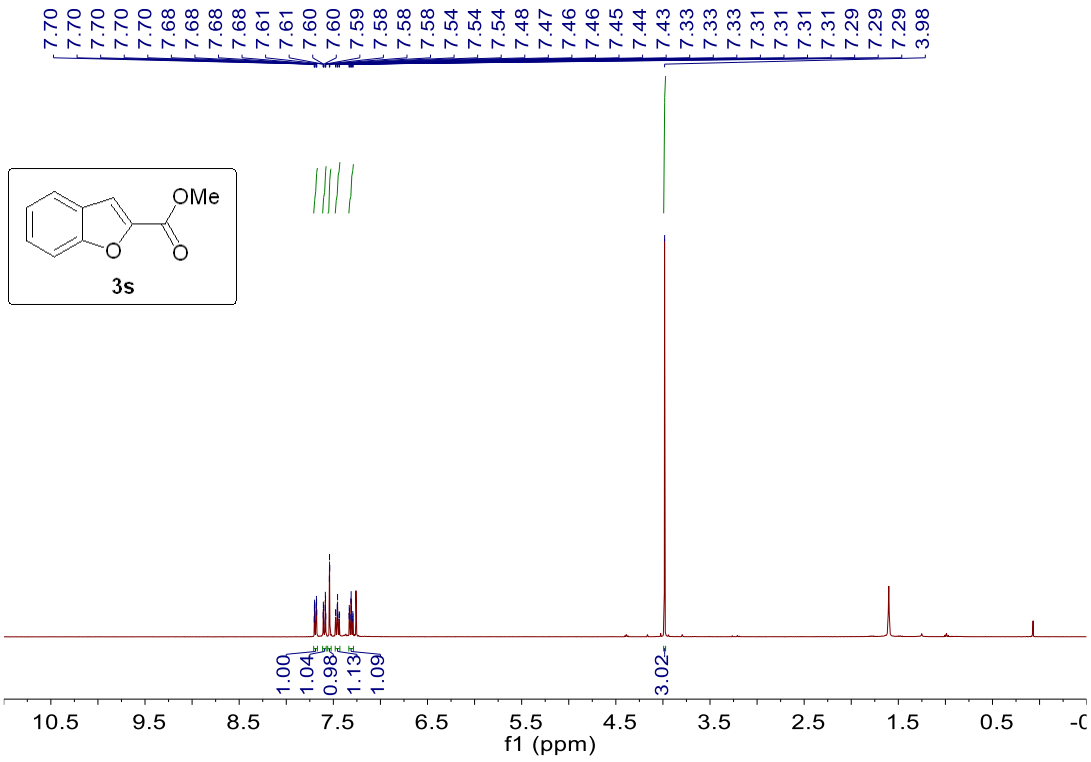
^{1}H NMR (400 MHz) spectrum of **3p** ($CDCl_3$, rt).



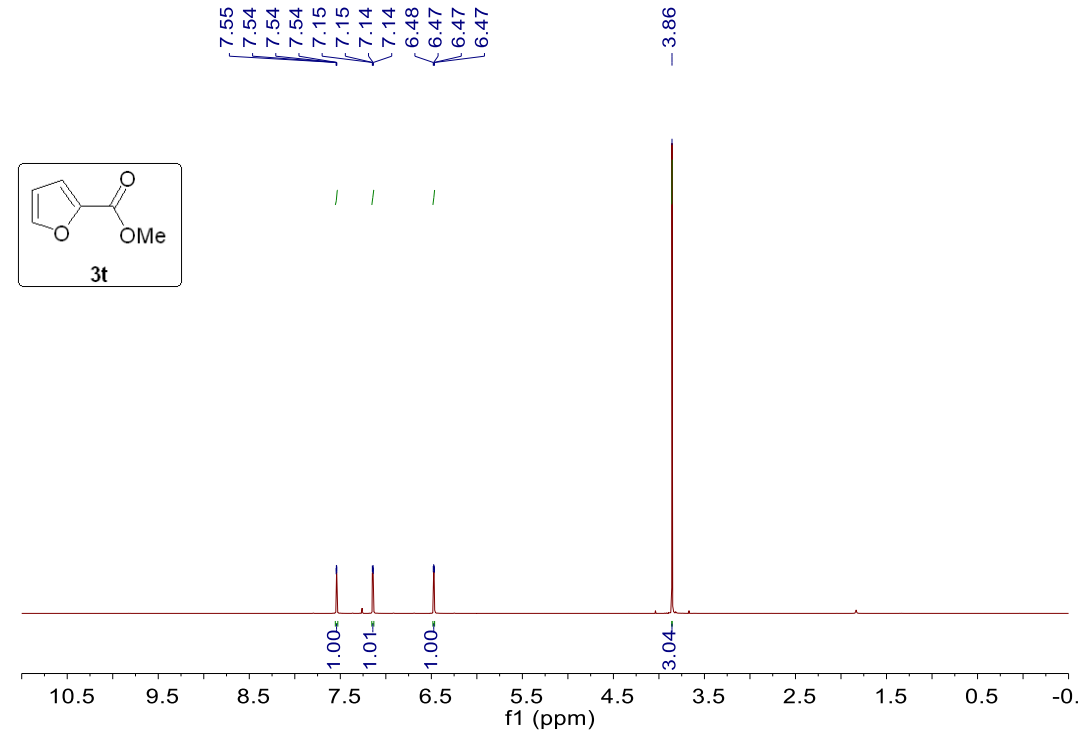
^{1}H NMR (400 MHz) spectrum of **3q** ($CDCl_3$, rt).



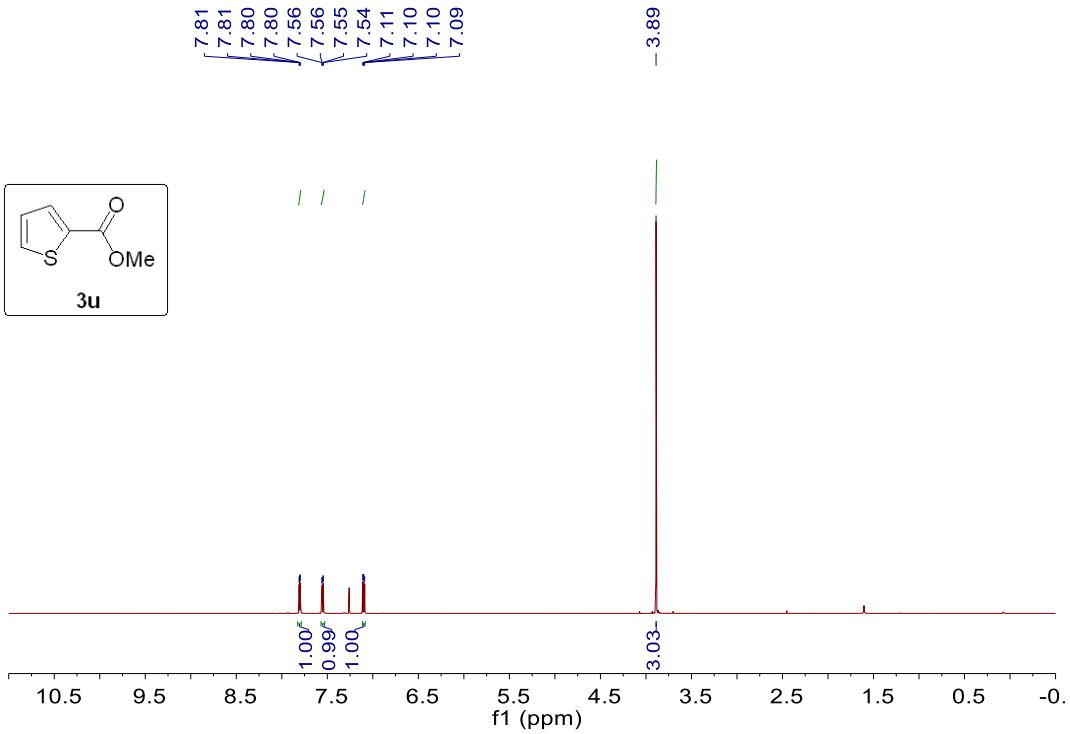
^{1}H NMR (400 MHz) spectrum of **3r** ($CDCl_3$, rt).



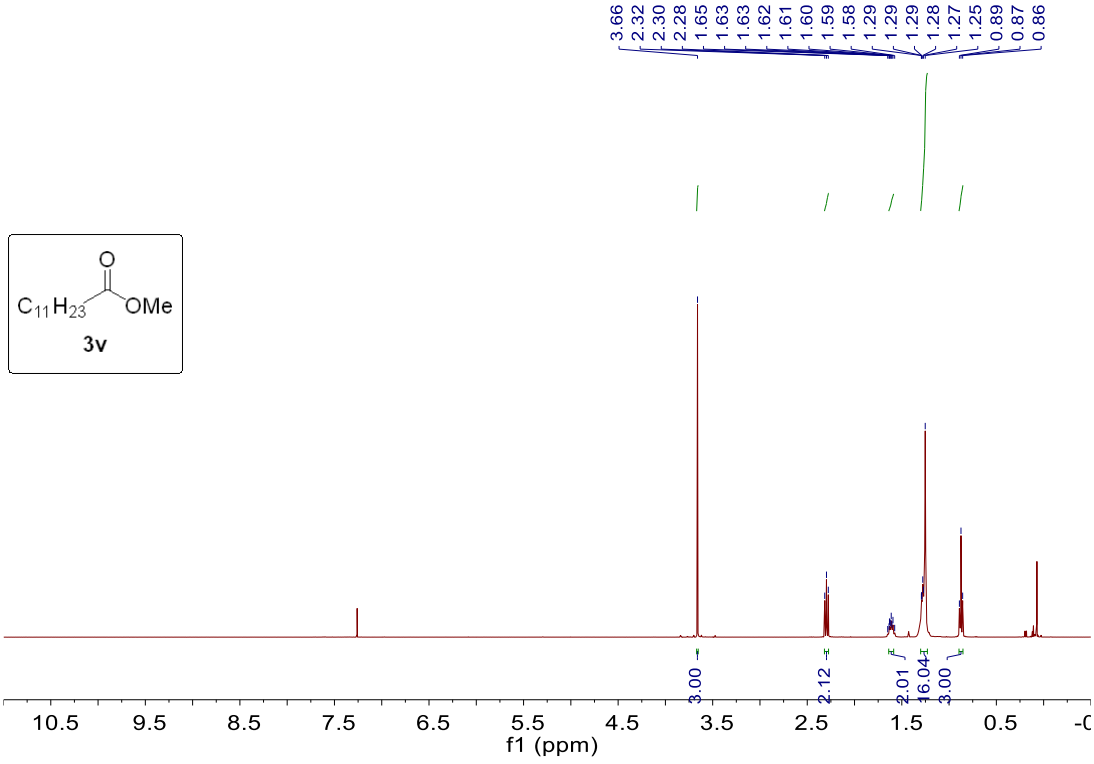
^{1}H NMR (400 MHz) spectrum of **3s** ($CDCl_3$, rt).



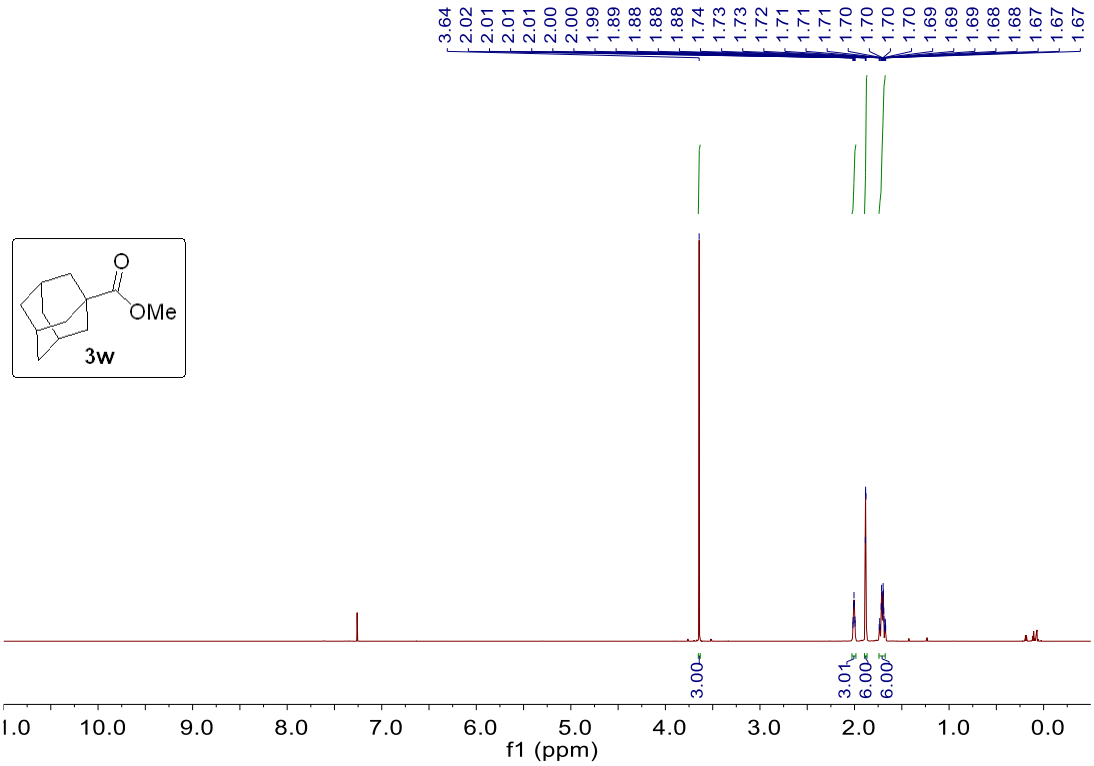
^{1}H NMR (400 MHz) spectrum of **3t** ($CDCl_3$, rt).



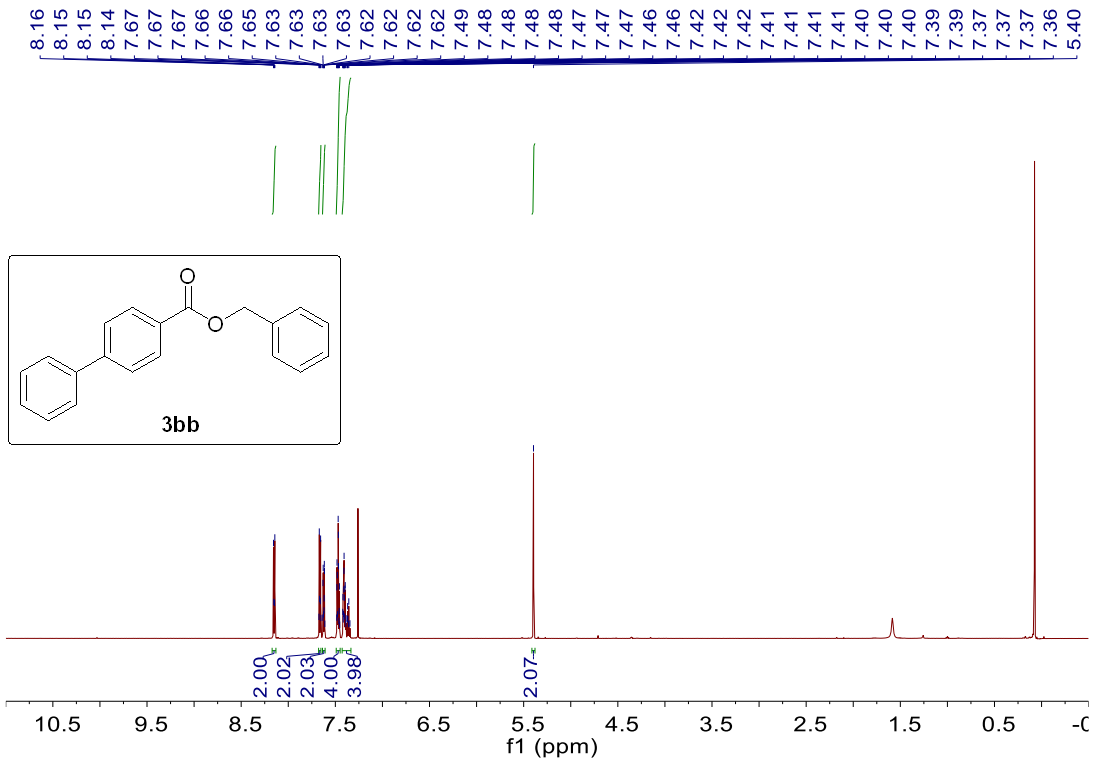
^{1}H NMR (400 MHz) spectrum of **3u** ($CDCl_3$, rt).



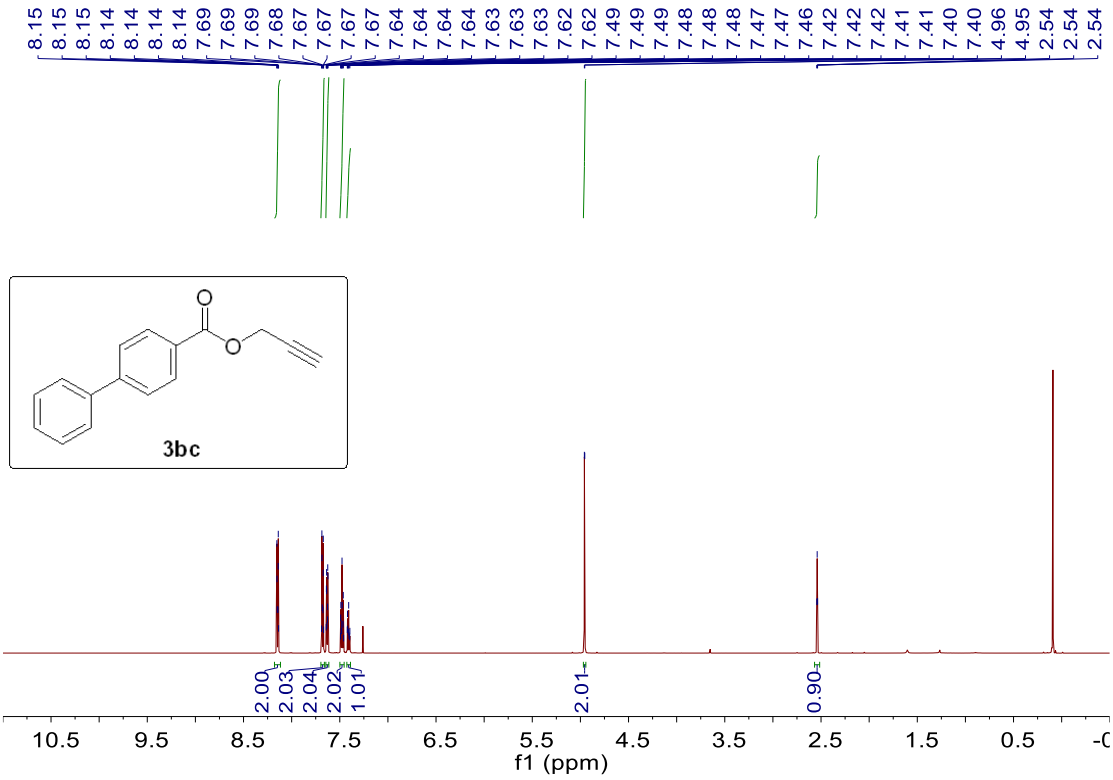
^{1}H NMR (400 MHz) spectrum of **3v** ($CDCl_3$, rt).



^{1}H NMR (600 MHz) spectrum of **3w** ($CDCl_3$, rt).



^{1}H NMR (600 MHz) spectrum of **3bb** ($CDCl_3$, rt).



^{1}H NMR (600 MHz) spectrum of **3bc** ($CDCl_3$, rt).

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Conclusion

Conclusion

In this PhD Thesis, the Author described the transformation of acyl halides, synthetic protocols for conversion of carboxylic acid derivatives into valuable adducts, particularly, nitriles, arylboronates, and esters. Since acyl chlorides are commercially available or could be easily prepared from the corresponding carboxylic acids, nickel-catalyzed cyanation of acyl chlorides were studied. The method can be applicable to the synthesis of an array of nitrile compounds bearing a wide range of functional groups under mild and neutral conditions. The step-by-step experimental studies revealed that the reaction sequences of the present catalytic reaction are oxidative addition, transmetalation, decarbonylation, and reductive elimination. Nickel-catalyzed decarbonylative borylation of acyl fluorides with bis(pinacolato)diboron were investigated, which is capable of producing various aromatic boronates. Methoxylation of acyl fluorides with cyclopentyl methyl ether (CPME) mediated by tetrabutylammonium difluorotriphenysilicate (TBAT) via regiospecific C–OMe bond cleavage was described, in which cyclopentyl methyl ether as a potential methoxylating agent. This PhD Thesis provides conversional and efficient methods to convert easily available carboxylic acids to valuable adducts nitriles, organoboronates as well as esters.

Chapter 2. Nickel-Catalyzed Decarbonylative Cyanation of Acyl Chlorides

In Chapter 2, the Author focus on the nickel-catalyzed decarbonylative cyanation of acyl chlorides with trimethylsilyl cyanide (TMSCN). The in-situ formation of acyl chlorides from the corresponding abundant carboxylic acids realized the synthesis of an array of useful organonitriles, some of which include bioactive molecules. The present cyanation proceeded in a complete decarbonylative manner under mild and neutral conditions. Therefore, various functional groups such as ether, ester, ketone, trifluoromethyl, cyano, methylthio, and even highly reactive bromo and iodo groups were well tolerated. Besides, the secondary and tertiary alkylated acyl chlorides were well accommodated under optimized reaction conditions.

This Chapter demonstrates not only synthetic utility but mechanistic insights into the nickel-catalyzed decarbonylative cyanation of aroyl chlorides. Although transition-metal-catalyzed decarbonylative cross-coupling have been further explored,

reaction mechanism of the sequence of reactions is still under debate. In this Chapter, the sequences of the reaction were well investigated by step-by-step stoichiometric experiments. Initially, a rapid oxidative addition of an acyl chloride to nickel(0) species was observed, regardless of PPh_3 or PEt_3 was used as the ligand, whereas the electron-donating ability of the phosphine ligands is crucial for the decarbonylation and reductive elimination steps. In the case of PPh_3 in a stoichiometric reaction at room temperature, both oxidative addition and subsequent decarbonylation/transmetalation can readily occur due to a weak coordination ability of PPh_3 to a nickel center, and a smooth reductive elimination was observed. In a sharp contrast, when PEt_3 was used as the ligand, the oxidative adduct was not prone to release CO in the absence of TMSCN, which renders the isolation of the acyl(chloro)nickel complex, *trans*-Ni(1-NpCO)Cl$(PEt_3)_2$ possible. In the presence of TMSCN, transmetalation occurred prior to decarbonylation, but the intermediate *trans*-Ni(1-Np)CN$(PEt_3)_2$ was found to be unreactive to reductive elimination, even at the elevated temperature of 80 ºC. The step-by-step experimental studies revealed that the reaction sequences of the present catalytic reaction are oxidative addition, transmetalation, decarbonylation, and reductive elimination.

Chapter 3. Nickel-Catalyzed Decarbonylative Borylation of Acyl Fluorides

In this Chapter, a series of arylboronates were successfully synthesized. Arylboronates bearing various functional groups were readily obtained from acyl fluorides. Acyl fluorides are easily prepared from carboxylic acids or acyl chlorides with organofluorine agents or inorganic alkali metal fluorine salts. With these synthesized acyl fluorides, the first $Ni(cod)_2/PPh_3$ catalyst system has been established for decarbonylative borylation of acyl fluorides with bis(pinacolato)diboron. The utilization of the newly developed method is capable of activating a wide range of acyl fluorides including commercially available drug for decarbonylative borylation to produce various organoboronates, which contributes to promising perspectives for the synthesis of functional materials and pharmaceuticals.

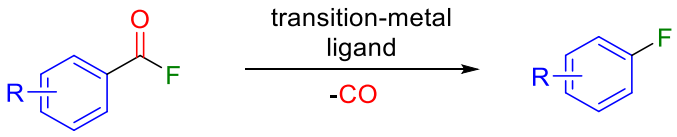
Chapter 4. PPh_3-Assisted Esterification of Acyl Fluorides with Ethers via C(sp^3)−O Bond Cleavage Accelerated by TBAT

In Chapter 4, the Author described methoxylation of acyl fluorides with commonly used

solvent, cyclopentyl methyl ether (CPME) mediated by TBAT via cleavage of a relatively unreactive C−O bond. Notably, in all examples for demethylation reported, a methyl group played as a protecting group of a hydroxyl group. To the best of his knowledge, this is the first study of C−O bond cleavage of aliphatic ethers releasing methoxy group sources in organic transformations. This protocol was distinguished by its metal-free, and mild conditions, which rendered various functional groups such as methoxy, trifluoromethyl, cyano and methoxycarbonyl, even relatively highly reactive chloro group were well tolerated. For substrates, not only acyl fluorides but also heteroacyl fluorides could afford good results. With investigation of the substrate scope for ethers, several symmetrical and unsymmetrical benzyl and propargyl group-containing ethers were proven to be good reaction partners in this transformation. In addition, the primitive mechanistic insights revealed that a C−O bond was cleaved through the hypervalent silicate species. Meanwhile, acyl fluoride reacts with PPh_3 to generate phosphonium which must be more electrophilic to participate in methoxylation with the formed fluoride-assisted nucleophilic attack of a methoxide ion to a carbonyl group, giving the desired products. From a viewpoint of the synthetic utility, the present method shown in this Chapter can provide a significant contribution to synthetic organic chemistry.

Future Perspective

Acyl fluorides could server as versatile building blocks including acyl, aryl, and fluorine sources. Acyl fluorides were found to act as the acylation fragment in transition-metal-catalyzed Negishi, Hiyama, Suzuki-Miyara, reduction, and acylation to give ketones and aldehydes without a CO loss. The transformation of acyl fluorides via decarbonylative alkylation, borylation, stannylation, arylation, silylation, and other reactions were studied, in which acyl fluorides used as the aryl source. However, the utilization of such molecules as the acyl and fluorine moieties has been less studies, particularly, acyl fluorides serving as both aryl and fluorine sources has been virtually unexplored. In the future, the decarbonylative fluorination of acyl fluorides might potentially be used as a novel approach to generate organic fluorinated compounds.



List of Publications

Publications Related to the Ph.D Thesis

Chapter 2

1) Nickel-Catalyzed Decarbonylative Cyanation of Acyl Chlorides
Zhenhua Wang, Xiu Wang, Yasuyuki Ura, and Yasushi Nishihara
Org. Lett. **2019**, *21*, 6779-6784.

Chapter 3

2) Nickel-catalysed decarbonylative borylation of aroyl fluorides
Zhenhua Wang, Xiu Wang, and Yasushi Nishihara
Chem. Commun. **2018**, *54*, 13969-13972.

Chapter 4

3) PPh_3-Assisted Esterification of Acyl Fluorides with Ethers via C(sp^3)–O Bond Cleavage Accelerated by TBAT
Zhenhua Wang, Xiu Wang, and Yasushi Nishihara
Catalysts **2019**, *9*, 574.

Other Publications

4) Synthesis of 2-Substituted Propenes by Bidentate Phosphine Assisted Methylenation of Acyl Fluorides and Acyl Chlorides with $AlMe_3$
Xiu Wang, Zhenhua Wang, Yuya Asanuma, and Yasushi Nishihara
Org. Lett. **2019**, *21*, 3640-3643.

5) Nickel-Catalyzed Decarbonylative Stannylation of Acyl Fluorides under Ligand-Free Conditions
Xiu Wang, Zhenhua Wang, Li Liu, Yuya Asanuma, and Yasushi Nishihara
Molecules **2019**, *24*, 1671.

6) Nickel/Copper-Catalyzed Decarbonylative Silylation of Acyl Fluorides
Xiu Wang, Zhenhua Wang, and Yasushi Nishihara
Chem. Commun. **2019**, *55*, 10507-10510.

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Nickel-Catalyzed Decarbonylative Cyanation of Acyl Chlorides

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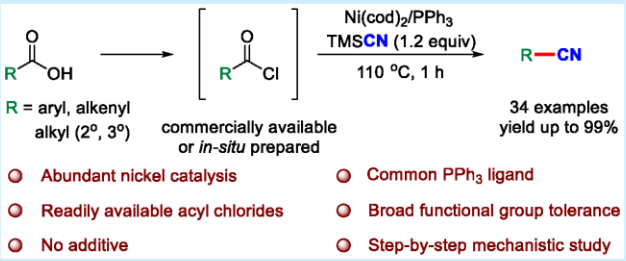
Supporting Information

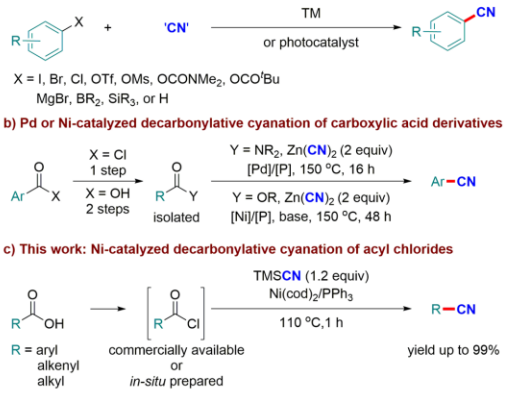


ABSTRACT: Ni-catalyzed decarbonylative cyanation of acyl chlorides with trimethylsilyl cyanide has been achieved. This transformation is applicable to the synthesis of an array of nitrile compounds bearing a wide range of functional groups under neutral conditions. The step-by-step experimental studies revealed that the reaction sequences of the present catalytic reaction are oxidative addition, transmetalation, decarbonylation, and reductive elimination.

Nitriles are prevalent in natural products, pharmaceuticals, agrochemicals, dyes, and herbicides[1] as well as important intermediates.[2] In particular, arylnitriles can be obtained via the classical methods of Sandmeyer[3] and Rosenmund−von Braun[4] reactions by the treatment of diazonium salts or aryl halides with CuCN, and various synthetic routes to arylnitriles have been further developed.[5−7] Alternatively, transition-metal (TM)-catalyzed nucleophilic cyanation of "preactivated" aryl halides[8] and phenol derivatives[9] and electrophilic cyanation of organometallic reagents[10] with various CN sources have well been developed (Scheme 1a). Higher atom-economy cyanation of arene C−H bonds by TM-catalyzed,[11] TM-mediated,[12] or photoinduced[13] reactions with the aid of suitable directing groups or electron-rich (hetero)arenes has been achieved.

On the contrary, carboxylic acids are potential candidates as electrophiles because they are naturally abundant and readily available.[14] However, the direct transformation of carboxylic acids and their derivatives to nitriles has various drawbacks, for example, the requirement of additional preparatory steps, the use of excess reagents, harsh conditions, and the narrow range substrates.[15] Recently, two pioneering studies on decarbonylative cyanation have been disclosed (Scheme 1b). Szostak demonstrated the Pd-catalyzed decarbonylative cyanation of amides with $Zn(CN)_2$, affording a wide range of arylnitriles.[16] Subsequently, Rueping developed the Ni-catalyzed cyanation of phenolic esters or amides with $Zn(CN)_2$ in which 2 equiv of base were required to reach higher yields.[17] However, all of the starting materials, amides, and esters in the above-mentioned

Scheme 1. Synthetic Routes for Nitriles



reactions need to be presynthesized from the corresponding acyl chlorides. Therefore, a direct and mild protocol of decarbonylative cyanation of acyl chlorides to nitriles is of great interest because acyl chlorides are commercially available

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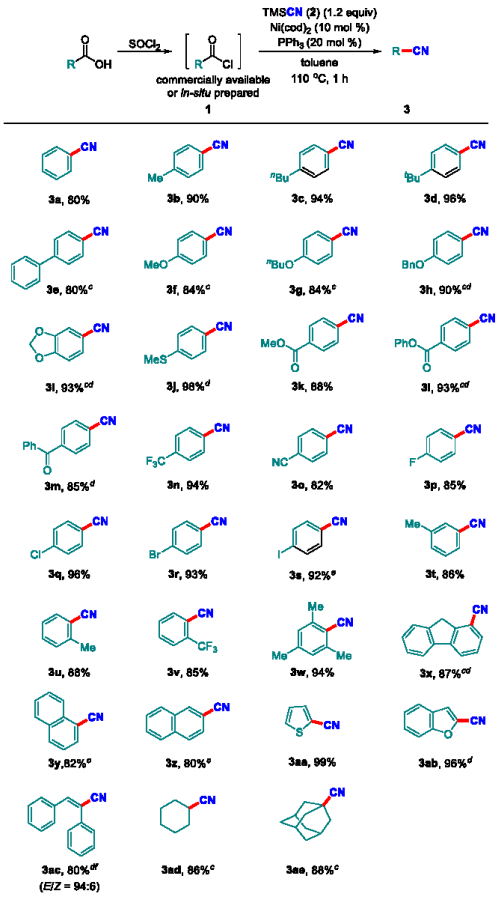
or could be easily prepared from the abundant carboxylic acids.[18] Although catalytic decarbonylative-type reactions of acyl chlorides could accommodate transformations for C−X bond construction,[19] including arylation,[20] chlorination,[21] silylation,[22] Mizoroki−Heck reaction,[23] and difluoromethylation,[24] to the best of our knowledge, decarbonylative cyanation of acyl chlorides has been virtually unexplored. In our continuing interests in the nickel-catalyzed decarbonylative transformation of acyl halides,[25] we herein report the establishment of an efficient and practical synthetic method of nitriles from carboxylic acids via acyl chlorides (Scheme 1c).

We commenced the model reaction of benzoyl chloride (**1a**) with trimethylsilyl cyanide (TMSCN, **2**) as the substrates. After the extensive optimization of reaction parameters (Tables S1−S10), an inexpensive catalytic system of $Ni(cod)_2$ and PPh_3 effectively facilitated the decarbonylative cyanation of **1a** to afford benzonitrile (**3a**) in 80% yield (Table S10, entry 1). Notably, the exogenous base was not necessary, and this transformation could afford satisfying yields of the corresponding nitriles at 110 °C within 1 h. The previously reported palladium- or nickel-catalyzed decarbonylative cyanation of carboxylic acid derivatives required an extended reaction time (16−48 h) and high temperature (150 °C).[16,17] Although triphenylphosphite gave benzonitrile (**3a**) in 72% yield (Table S10, entry 2), monodentate phosphine ligands such as PEt_3, $PnBu_3$, or PCy_3 were found to be inferior (Table S10, entries 3−5). These ligand effects indicate that less electron-donating phosphine ligands are highly suitable for the present reaction regardless of the cone angles. $Zn(CN)_2$ that has been successfully used in the Ni- or Pd-catalyzed decarbonylative cyanation reaction[16,17] gave no products. Because no formation of benzoyl cyanide was detected, the highly selective formation of **3a** rather than benzoyl cyanide might be a consequence of the unfavorable reductive elimination between the benzoyl group and the cyano group, both of which are electron-poor ligands. Decarbonylation triggers reductive elimination between an electron-rich aryl ligand and an electron-deficient cyano ligand by a favorable electronic synergy.

The optimized reaction conditions were applied for various acyl chlorides, and the results are summarized in Scheme 2. It is noteworthy that the acyl chlorides used were not only commercially available but in situ prepared from corresponding carboxylic acids for the one-pot protocol (denoted as footnote *d*), which demonstrates a practicability of the present transformation. Initially, a qualitative assessment of the electronic trend of the decarbonylative cyanation reaction was examined. Electron-donating alkyl groups installed in the *para* position of acyl chloride could give the corresponding nitriles **3b−d** in 90−96% yield. When the substrates bearing ether **3f−h** and acetal **3i** groups were employed, the higher temperature was required to gain satisfying results. Methylthio (**3j**), methoxycarbonyl (**3k**), phenoxycarbonyl (**3l**), and benzoyl (**3m**) groups were well tolerated to give the desired products in good to excellent yield. On the contrary, a series of electron-deficient *para*-substituted acyl chlorides having trifluoromethyl, cyano, and halogens smoothly furnished **3n−s** in 82−96% yield. Although bromide and iodide are known to be reactive for oxidative addition to nickel catalysts, they were compatible during the reactions. Sterically hindered *ortho* substituents were also productive for the formation of arylnitriles **3u** and **3v**, regardless of the electronic nature of the substituents. Even more sterically hindered 2,4,6-trimethylbenzoyl chloride (**1w**) was efficiently converted into

Scheme 2. Nickel-Catalyzed Decarbonylative Cyanation[a,b]



[a]Reaction conditions: acyl chlorides **1** (0.2 mmol), TMSCN (**2**, 0.24 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.04 mmol), toluene (1 mL), 110 °C, and 1 h. [b]Isolated yield. [c]150 °C, 1 h. [d]Corresponding carboxylic acid (0.2 mmol) was used. [e]80 °C, 1 h. [f]**1ac** (*E*/*Z* 94:6) was used.

3w in 94% yield. Fused aromatic acyl chlorides (**1x−z**) could be incorporated and gave the corresponding arylnitriles in 80−87% yield at the elevated temperature. It should be noted that heteroatom-containing acyl chlorides also participated in the reaction, furnishing the desired nitriles **3aa** and **3ab** in 99 and 96% yield, respectively. Strikingly, the reaction scope could be readily extended to the synthesis of α,β-unsaturated nitriles (**3ac**). More surprisingly, secondary (**1ad**) and tertiary (**1ae**) alkylated acyl chlorides were proved to be an ideal coupling partner, although primary counterparts were unsuccessful; lauroyl chloride gave only 17% of the corresponding nitrile under standard conditions.

To demonstrate the synthetic utility of the present reaction, the decarbonylative cyanation of biologically active compounds was conducted. Cyanation of probenecid,[26] a carboxylic-acid-containing drug, was viable and gave **3af** in 92% yield (Scheme

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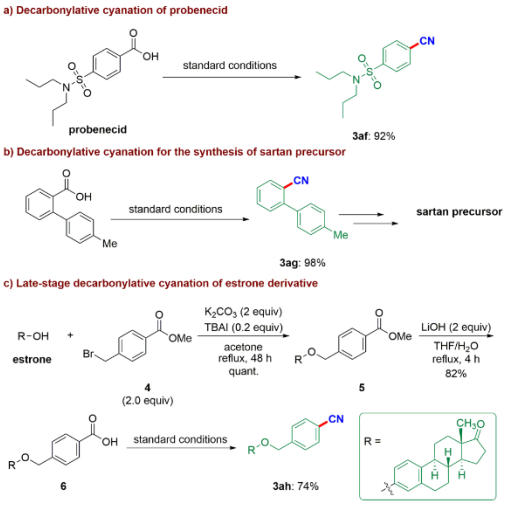
3a). A key intermediate in the synthesis of sartan derivatives,[27] 2-(4-tolyl)benzonitrile (**3ag**), was isolated in 98% yield

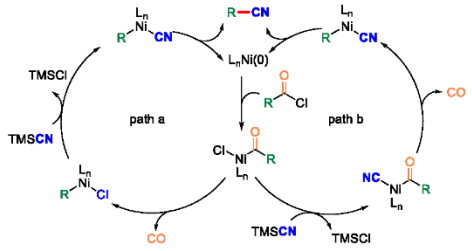
Scheme 3. Synthetic Applications



(Scheme 3b). Besides, we succeeded in the late-stage modification of a bioactive estrone derivative. The etherification of estrone with **4**, followed by the hydrolysis of **5** afforded carboxylic acid **6**. Finally, compound **6** was subjected to decarbonylative cyanation to provide **3ah** in 74% yield (Scheme 3c).

To date, reaction sequences for transition-metal-catalyzed decarbonylative couplings are still under debate. Two possible reaction pathways for the present reaction are shown in Scheme 4. In both pathways, the initial oxidative addition of

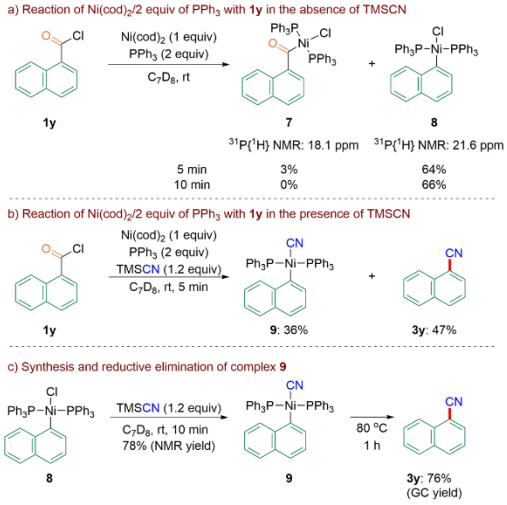
Scheme 4. Two Possible Reaction Pathways



acyl chloride to Ni(0) forms an acyl(chloro)nickel(II) species,[28] and the final reductive elimination affords the product. In path a, CO elimination takes place prior to transmetalation with TMSCN, which was supported by Shi[29] and Sanford.[30] They conducted stoichiometric reactions to isolate acyl(halogeno)nickel(II) complexes, leading to a smooth decarbonylation process. In addition, theoretical calculations performed by Szostak also illustrated that the acylpalladium species is prone to decarbonylation.[31] Alternatively, path b involves the reaction sequences of the transmetalation of the acyl(chloro)nickel(II) complex with TMSCN prior to decarbonylation. Ritter[24] also showed experimental evidence for supporting path b by isolation of the intermediate complexes in the Pd-catalyzed decarbonylative difluoromethylation. Furthermore, Itami,[32] Rueping,[33] and Schoenebeck[34] performed density functional theory (DFT) calculations in which a lower energy barrier is required for a smooth decarbonylation of the intermediates than for transmetalation.

To clarify which pathway in Scheme 4 is more favorable, we carried out some stoichiometric reactions. Initially, the reaction of $Ni(cod)_2$ and 2 equiv of PPh_3 with 1-naphthoyl chloride (**1y**) in C_7D_8 was monitored by the $^{31}P\{^1H\}$ NMR measurements at room temperature (Scheme 5a). After 5

Scheme 5. Mechanistic Studies Using PPh_3 as the Ligand



min, a singlet at δ 18.1 assigned to acyl(chloro)nickel(II) complex **7** was observed in only 3% yield, which completely disappeared after 10 min, whereas 64% of aryl(chloro)nickel(II) complex **8** (δ 21.6) and 33% of $Ni(CO)_2(PPh_3)_2$ (δ 32.9) were detected. This result suggests that both oxidative addition and subsequent decarbonylation can readily occur due to a weak coordination ability of PPh_3, which possesses an open coordination site to accept the carbonyl ligand.

Given that no reaction took place between **1y** and TMSCN, we performed the identical reaction in the presence of TMSCN at room temperature (Scheme 5b). After 5 min, complex **9** was detected in 36% NMR yield, along with the formation of **3y** in 47% yield, suggesting that the rates of both transmetalation and decarbonylation are faster than that of reductive elimination, leading to the product **3y**.

Alternatively, complex **9** was prepared by the reaction of the once prepared complex **8**, derived from the reaction of $Ni(cod)_2$, 2 equiv of PPh_3, and **1y**, with TMSCN. Heating the toluene solution of complex **9** to 80 °C for 1 h smoothly afforded **3y** in 76% yield through reductive elimination (Scheme 5c). When the same reaction was conducted in the presence of 2 equiv of PPh_3, the yield of the product **3y** was dropped to 50%. These results strongly support the notion that the reductive elimination takes place by ligand dissociation to

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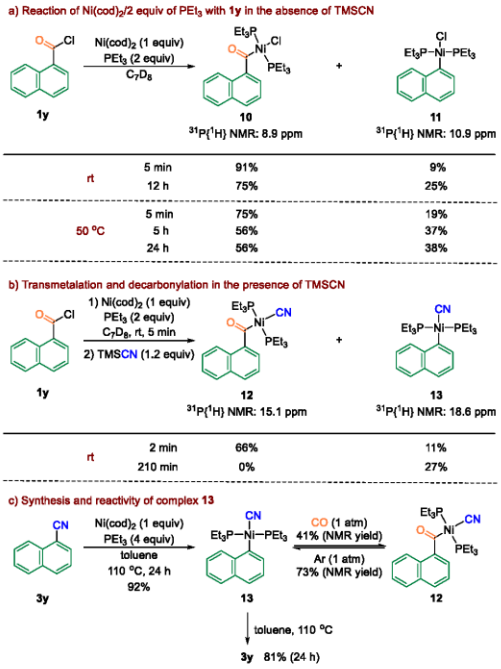
form a three-coordinate complex rather than proceeding from a four-coordinate intermediate.

To verify the effect of the phosphine ligands, we conducted the identical stoichiometric reactions using PEt_3 (Scheme 6a).

Scheme 6. Mechanistic Studies Using PEt_3 as the Ligand



Similarly, the oxidative addition of **1y** to nickel was completed at room temperature within 5 min, and acyl(chloro)nickel(II) complex **10** was observed in 91% yield, along with aryl-(chloro)nickel(II) complex **11** in 9% yield. Although this solution was kept for 12 h, 75% of complex **10** still remained intact. The same reaction was conducted at 50 °C, but no further decarbonylation occurred, even after 24 h. These results indicate the presence of an equilibrium between **10** and **11** and relatively unfavorable decarbonylation from **10** rather than **7**. To our delight, acyl(chloro)nickel complex **10** could be isolated in 45% yield, and its structure was unambiguously determined by X-ray analysis (Figure 1a).

Next, we investigated the reaction of the Ni(0) precursor with **1y** in the presence of TMSCN (Scheme 6b). The mixture of $Ni(cod)_2$, 2 equiv of PEt_3, and **1y** in C_7D_8 was stirred at room temperature for 5 min. Upon the addition of TMSCN, complex **10** was converted to produce complex **12** immediately in 66% yield. Complex **12** was then gradually converted to complex **13** in 27% yield via decarbonylation over 210 min, albeit with other unidentified major products bearing two PEt_3 ligands (22% combined yields). Besides, an insoluble solid was observed at the bottom of an NMR tube. With the results shown in Scheme 6a,b in hand, we concluded that transmetalation with TMSCN is faster than decarbonylation with a PEt_3 ligand.

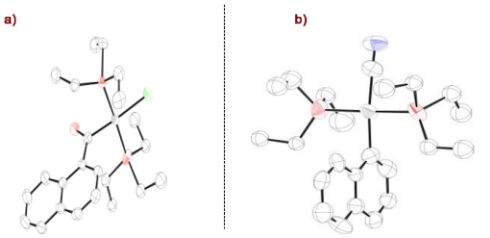
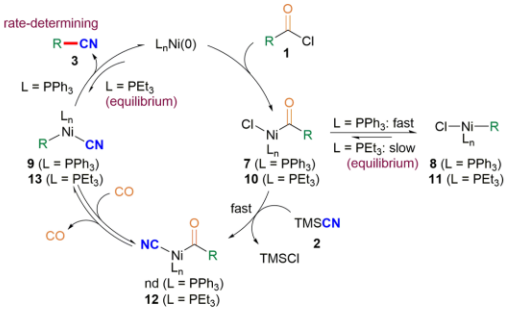


Figure 1. X-ray crystal structure of complexes (a) **10** and (b) **13**. ORTEP drawings with atoms at 50% probability. Hydrogen atoms are omitted for clarity. A PEt_3 ligand was treated as disordered.

Complex **13** could also be synthesized by oxidative addition of **3y** to $Ni(cod)_2$/4 PEt_3 in 92% NMR yield (Scheme 6c).[35] Upon heating complex **13** at 110 °C for 24 h, reductive elimination product **3y** was obtained in 81% yield. Although this observation is inconsistent with the result that a catalytic reaction did not proceed when PEt_3 was employed, no CO-coordinated Ni-complex was detected at all. Due to the robustness of the aryl(cyano)nickel(II) complex **13**, its X-ray analysis was successful (Figure 1b). Treatment of the toluene solution of complex **13** with CO gas in a balloon, complex **12** was detected in 41% NMR yield, along with the remaining complex **13** in 36% yield, while upon the replacement of CO with Ar, complex **13** was recovered in 73% NMR yield, indicating that a decarbonylation process is reversible.

On the basis of our experimental studies, we propose the mechanism of the present reaction (Scheme 7). Initially, the

Scheme 7. Proposed Mechanism



oxidative addition of acyl chlorides **1** to Ni(0) generates the acyl(chloro)nickel(II) intermediate **7** (L = PPh_3) or **10** (L = PEt_3). In the absence of **2**, the reaction rate of the decarbonylation of complex **7** leading to **8** is much faster than that of the conversion of complex **10** to **11**, whereas in the presence of **2**, although both transmetalation and decarbonylation are too fast to detect in the PPh_3 system, the transmetalation of acyl(chloro)nickel(II) **10** takes place to produce complex **12** prior to decarbonylation, forming complex **13** in the PEt_3 system. The fact that the lifetime of complex **9** was observed to some extent suggests that reductive elimination might be a rate-determining step in the catalytic cycle, although other possibilities such as the CO loss to regenerate the active Ni(0) catalyst cannot be ruled out.

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In summary, we have developed the decarbonylative cyanation of easily available acyl chlorides under nickel catalysis. This reaction can readily transform diverse acyl chlorides into nitriles with a broad substrate scope and functional group tolerance. Detailed mechanistic studies clarified the sequences of the reaction in the catalytic cycle. The utilization of a weaker coordinating PPh_3 ligand is crucial to facilitate both decarbonylation and reductive elimination steps.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02398.

Experimental procedures, characterization of new compounds, and spectroscopic data (PDF)

Accession Codes

CCDC 1909903−1909904 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Nickel-catalysed decarbonylative borylation of aroyl fluorides†

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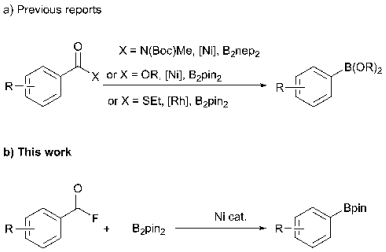
The first $Ni(cod)_2/PPh_3$ catalyst system has been established for decarbonylative borylation of aroyl fluorides with bis(pinacolato)-diboron. A wide range of functional groups in the substrates were well tolerated. The ease of access of the starting aroyl fluorides indicates that these results might become an alternative to the existing decarbonylation events.

Arylboronic acids and arylboronates are versatile synthetic reagents in synthetic organic chemistry.[1] These compounds are conventionally synthesized by organolithium or magnesium compounds, which are not compatible with functional groups.[2] The further development of transition-metal-catalysed borylation reactions has allowed the synthesis of arylboronates from numerous aryl iodides, bromides, chlorides, or triflates.[3] In recent years, much effort has been devoted to the synthesis of arylboronates *via* C–X (X = H,[4] halogen,[5] SR,[6] OR,[7] CN,[8] or NR_2[9]) bond activation.

Taking into account the growing concerns on the environmental and sustainable events of our society, carboxylic acid as an aromatic feedstock alternative is in high demand. In particular, facile diversification of carboxylic acids into organoboron compounds shows high value.[10] As such, several attempts have succeeded in the transformation of carboxylic acid derivatives such as amides,[11,12] esters,[13–15] thioesters,[16,17] and chloride[18] into the corresponding arylboronates in a decarbonylative manner (Scheme 1a). Very recently, the decarboxylative borylation of aliphatic and aromatic *N*-hydroxyphthalimide esters, derived from the corresponding carboxylic acids, were also disclosed.[19]

On the other hand, aroyl fluorides easily prepared from the corresponding carboxylic acids,[20] arguably one of the simplest and most atom-economical derivatives in the aroyl acid series, have received considerably less attention, presumably due to their low reactivity. In some cases, however, aroyl fluorides were found to be a cross-coupling partner with organozinc,[21] -silicon,[22] and -boron[23] nucleophiles to generate various ketones without decarbonylation. Recently, Ogiwara and Sakai reported palladium-catalysed reduction of sp^2 and sp^3 acid fluorides in a retentive or decarbonylative manner.[24] This report suggested that the retentive or decarbonylative pathway could be controlled by the ligands employed. Encouraged by the decarbonylative C–C bond formation, namely, trifluoromethylation of acid fluorides under a $[(cinnamyl)PdCl]_2$/xantphos catalytic system,[25] we also disclosed decarbonylative alkylation of aroyl fluorides catalysed by $Ni(cod)_2$/DPPE.[26] To the best of our knowledge, however, the decarbonylative borylation of acid fluorides has been virtually unexplored.[27] Herein we report our results on the utilization of aroyl fluorides as the electrophilic component in a nickel-catalysed decarbonylative borylation reaction (Scheme 1b).



Scheme 1 Decarbonylative borylation of carboxylic acid derivatives.

Our initial studies involved the evaluation of various ligands and bases in the borylation reaction of benzoyl fluoride (**1a**) with bis(pinacolato)diboron (**2a**, (B_2pin_2) catalysed by $Ni(cod)_2$ (Tables S1–S4, ESI†)). To our delight, 33% of desired product **3a** was obtained when a stable and inexpensive ligand PPh_3 was employed. Extensive screening of the reaction conditions (see the ESI†) revealed that a mixture of 10 mol% of $Ni(cod)_2$, 30 mol% of PPh_3, 2.5 equiv. of KF, and 2.0 equiv. of NaCl as the additive

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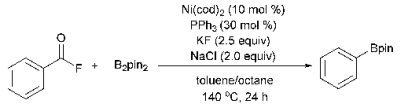
at 140 °C for 24 h in a mixed solvent system, toluene and octane (v/v = 2/1), provided the best result, affording **3a** in 83% yield (Table 1, entry 1). Other air-stable Ni(II) salts other than $Ni(cod)_2$ resulted in a lower yield of **3a** (entries 2 and 3). Palladium catalysts such as $Pd(OAc)_2$ and $Pd(dba)_2$ were inefficient (entries 4 and 5). Although $[Rh(OH)(cod)]_2$ was reported to be efficient in decarbonylative borylation of aromatic thioesters,[16] it showed moderate reactivity (entry 6). Replacement of PPh_3 with other monodentate phosphine ligands under identical reaction conditions decreased the yield (entries 7–9). Interestingly, the yield of **3a** was increased in the order of CsF < NaF < KF (Table S4, ESI†), suggesting that a countercation is important to some extent.[28] A similar tendency was observed in the additives; NaCl and KCl afforded good yields, while LiCl, CsCl and TBAC (tetrabutylammonium chloride) gave poor results (entries 10–13). This revealed that suitable countercations may play a vital role in this transformation. These results are associated with recent publications that demonstrate the important role of countercations in C–O bond activation in reactions of aryl ethers.[29] When no NaCl was added, the yield was slightly decreased to 67% (entry 14). No desired product was detected in the absence of $Ni(cod)_2$ or PPh_3 in the decarbonylative borylation process (entries 15 and 16). The KF additive was found to be essential to proceed the reaction (entry 17), suggesting that an external activator of B_2pin_2 is required. When we applied certain conditions to the analogous benzoyl chloride at 140 °C (entry 18) and even at room temperature, 50 °C, or 80 °C, no decarbonylative borylation product was detected. It is indicated that a fluoride moiety plays a crucial role and conversion of benzoyl fluoride *in situ* into benzoyl chloride in the presence of NaCl can be ruled out during this transformation.

With the optimized conditions in hand, the generality of the reaction was subsequently investigated (Table 2). A wide range of electronically and sterically diverse aroyl fluorides with bis(pinacolato)diboron (**2a**) were smoothly converted into the corresponding arylboronates. Aroyl fluorides bearing electron-donating alkyl and alkoxy groups in the *para*-position afforded arylboronates **3b**–**3f** in 50–82% yields. High chemoselectivity of this decarbonylative borylation was demonstrated by the synthesis of **3i** bearing the ester functionality unreacted. This result suggests that this methodology is complementary to the decarbonylative borylation of aromatic esters.[13–15] Moreover, the introduction of electron-withdrawing groups onto benzoyl fluoride led to a slight decrease in the yields of products **3k** and **3l**. Reaction of benzoyl fluoride with *ortho*-substituents under the identical reaction conditions proceeds smoothly to yield **3n**–**3p**. Naphthyl (**3q** and **3r**), anthracenyl (**3s**), and biphenyl (**3g**, **3m**, and **3t**)-containing arylboronates were successfully obtained in good to high yields. On the other hand, although the decarbonylative borylation using vinyl and benzyl precursors have been elucidated, no traces of the desired products **3** were detected.

To evaluate the utility of this decarbonylative borylation reaction, reactions of a series of diborons have been carried out (Table 3). Using bis(hexylene glycolato)diboron (**2b**) and bis(neopentyl glycolato)diboron (**2c**, B_2nep_2) instead of **2a** with benzoyl fluoride (**1a**) gave the corresponding arylboronates **4b** and **4c** in 54% and 55% yields, respectively. The reaction of

Table 1 Optimization of the reaction conditions[a]

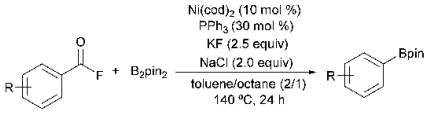


1a 2a 3a

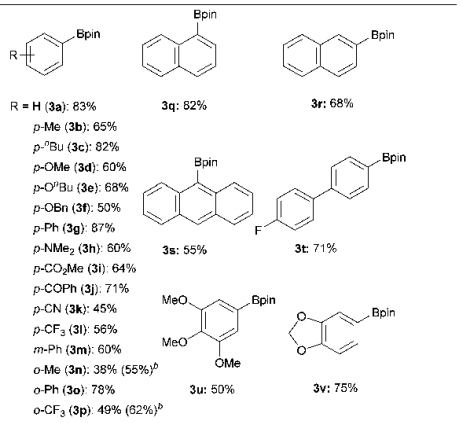
Entry	Deviation from standard conditions	Yield[b] (%)
1	None	85 (83)[c]
2	$NiCl_2$ instead of $Ni(cod)_2$	52
3	$Ni(OAc)_2{\cdot}4H_2O$ instead of $Ni(cod)_2$	4
4	$Pd(OAc)_2$ instead of $Ni(cod)_2$	16
5	$Pd(dba)_2$ instead of $Ni(cod)_2$	23
6	$[Rh(OH)(cod)]_2$ instead of $Ni(cod)_2$	50
7	PCy_3 instead of PPh_3	16
8	$P(OPh)_3$ instead of PPh_3	46
9	P^nBu_3 instead of PPh_3	71
10	LiCl instead of NaCl	5
11	KCl instead of NaCl	79
12	CsCl instead of NaCl	23
13	TBAC instead of NaCl	25
14	Without NaCl	67
15	Without $Ni(cod)_2$	0
16	Without PPh_3	0
17	Without KF	<1
18	Benzoyl chloride instead of **1a**	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h. [b] Determined by GC analysis. [c] An isolated yield is shown in parentheses.

Table 2 Decarbonylative borylation of aroyl fluorides[a,b]

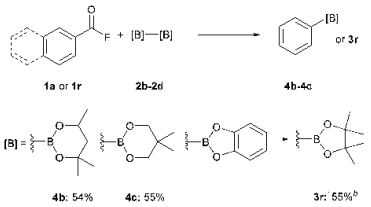


1a-1v 2a 3a-3v



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h. [b] $Ni(cod)_2$ (0.06 mmol), PPh_3 (0.18 mmol).

Table 3 Elucidation of other diborons[a,b]

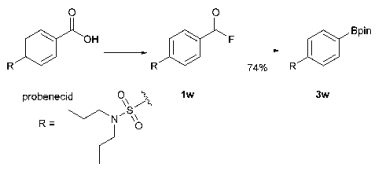


[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h. [b] **1r** (0.2 mmol), **2d** (0.4 mmol), then pinacol (4 equiv.) and NEt_3 (0.5 mL) at room temperature for 1 h.

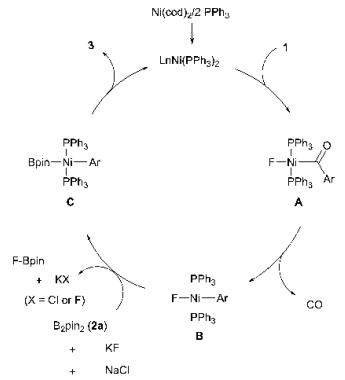
2-naphthoyl fluoride (**1r**) with bis(catecholato)diboron (**2d**, B_2cat_2), followed by the replacement with pinacol also yielded **3r** in 55% yield.

This nickel-catalysed decarbonylative borylation was also viable with complex molecular precursors bearing functional groups. For example, a carboxylic acid-containing drug, probenecid,[30] primarily used to treat gout and hyperuricemia, could be subjected to the two-step fluorination/decarbonylative borylation sequences. After fluorination of probenecid by conventional methods,[20c] aroyl fluoride **1w** was smoothly converted into the target arylboronate **3w** in 74% yield (Scheme 2),whereas the attempt to elucidate the one-pot synthesis of arylboronates without isolation of aroyl fluorides was found to be unsuccessful. To our delight, this decarbonylative borylation is applicable to a large-scale synthesis. The 10-mmol scale experiment provided 1.19 g of **3a** in 58% yield.

The proposed mechanism of decarbonylative borylation of aroyl fluorides is shown in Scheme 3. Initially, oxidative addition of aroyl fluorides to Ni(0) generates the acyl-nickel(II) intermediate **A**.[31–33] Although our attempt to isolate **A** was unsuccessful, we found some clues for arylnickel species **B**. The reaction of $Ni(cod)_2$/2 PPh_3 with benzoyl fluoride in C_6D_6 at rt provided a characteristic broad singlet at −409.9 ppm in the $^{19}F\{^1H\}$ NMR spectrum and a doublet at 15.1 ppm with a J_{P-F} of 44 Hz in the $^{31}P\{^1H\}$ NMR spectrum even after 1 h. Considering the results obtained by Sanford,[33] the formed oxidative adduct $Ni(COPh)F(PCy_3)_2$ caused decarbonylation to form $Ni(Ph)F(PCy_3)_2$ at room temperature within 10 min, in our case, the *in situ* generated $Ni(COPh)F(PPh_3)_2$ must be more unstable due to the weak coordination ability of PPh_3 than PCy_3. We thus concluded that



Scheme 2 Two-step borylation of probenecid.[a] [a]Reaction conditions: **1w** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h.



Scheme 3 Proposed mechanism.

the subsequent extrusion of carbon monoxide forming **B** could take place prior to transmetalation. Transmetalation between complex **B** and B_2pin_2 assisted by external KF (and NaCl) affords borylnickel(II) intermediate **C**. Finally, reductive elimination delivers the targeted arylboronates **3**, regenerating the Ni(0) species to complete a catalytic cycle.

In summary, we have developed the first decarbonylative borylation of aroyl fluorides with the assistance of an abundant and inexpensive metal Ni/PPh_3 catalytic system with B_2pin_2 as a coupling nucleophile, which is capable of producing various aromatic boronates. Importantly, this method realized that carboxylic acids can be converted into a wide array of arylboronates *via* aroyl fluorides. Currently, we are investigating the theoretical calculations to determine the reaction mechanism including a decarbonylation step, and other transition-metal-catalysed transformations of aroyl fluorides.

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Conflicts of interest

There are no conflicts to declare.

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PPh_3-Assisted Esterification of Acyl Fluorides with Ethers via C(sp^3)–O Bond Cleavage Accelerated by TBAT

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Abstract: We describe the (triphenylphosphine (PPh_3)-assisted methoxylation of acyl fluorides with cyclopentyl methyl ether (CPME) accelerated by tetrabutylammonium difluorotriphenysilicate (TBAT) via regiospecific C–OMe bond cleavage. Easily available CPME is utilized not only as the solvent, but a methoxylating agent in this transformation. The present method is featured by C–O and C–F bond cleavage under metal-free conditions, good functional-group tolerance, and wide substrate scope. Mechanistic studies revealed that the radical process was not involved.

Keywords: Acyl fluorides; cyclopentyl methyl ether (CPME); tetrabutylammonium difluorotriphenysilicate (TBAT); carbon-oxygen bond cleavage; esterification

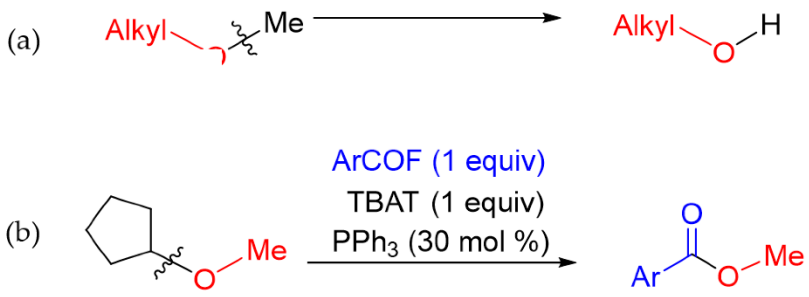
1. Introduction

The C–O bond cleavage in ethers is one of the most fundamental transformations in organic synthesis and has been widely applied in the manufacturing of fine chemicals as well as the synthesis of polyfunctional molecules [1–5]. Particularly, the preparation and degradation of ethers have often been considered important synthetic strategies for the protection/deprotection of hydroxyl groups. Although numerous studies on demethylation in aromatic methyl ethers have been reported [6–10], demethylation of viable aliphatic surrogates has been relatively less explored. Typically, various reagents have been utilized to convert aliphatic methyl ethers into the corresponding alcohols via demethylation (Scheme 1a), employing $BF_3{\cdot}Et_2O/(CH_3CO)_2O$ [11], BCl_3 [12], BBr_3 [13], $BF_3{\cdot}Et_2O/EtSH$ [14], Me_3SiI [15], hydrobromic acid/phase-transfer-catalysts [16], BBr_3/NaI/15-crown-5 [17], $(CH_3)_2BBr$ [18], $AlCl_3$/NaI/CH_3CN [19], or BI_3/*N*,*N*-diethylaniline [20].

On the other hand, since 2005, cyclopentyl methyl ether (CPME) [21,22] has become the common solvent in organic reactions [23–25]. Compared with other conventional ethereal solvents such as diethyl ether (Et_2O), tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), 1,4-dioxane, methyl *tert*-butyl ether (MTBE), and 2-MeTHF, CPME displays many advantages, such as low cost, high-boiling point (106 °C), low polarity, lower miscibility with water (1.1 g/100 g), low tendency to form peroxides, narrow explosion range, and stability under strong acidic and basic conditions. With these characteristics of CPME in mind, the utility of CPME as a potential reactant in various organic transformations are attractive. However, to the best of our knowledge, the selective C–O bond cleavage in CPME [26] and the utilization of released methoxy group as a methoxylating agent [27] has been unexplored.

Numerous examples for utilization of acyl fluorides in synthetic organic chemistry have been reported [28], while recently, unique reactivity of acyl fluorides has been extensively disclosed due to their strong electrophilicity and high stability [29,30]. Transformations of acyl fluorides into other

valuable molecules have been well demonstrated by others [31–36] and our group [37–40]. As a part of our ongoing interest in the functionalization of acyl halides, we herein report the nucleophilic methoxylation of acyl fluorides with CPME assisted by PPh_3 via both C–OMe and C–F bonds cleavage under metal-free conditions (Scheme 1b).

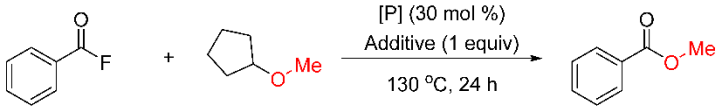


Scheme 1. C–O cleavage in alkyl methyl ethers. (**a**) Conventional demethylation of aliphatic methyl ethers (deprotection), (**b**) This work.

2. Results and Discussion

When we conducted the reaction of benzoyl fluoride (**1a**) with CPME (**2a**), giving rise to methyl benzoate (**3a**) in the presence of a catalytic amount of PPh_3, various additives were screened. As shown in Table, tetrabutylammonium difluorotriphenylsilicate (TBAT) [41] as the additive sufficiently increased the yield of **3a** in 74% yield (Table 1, entry 1). PPh_3 showed superior result than other monodentate phosphine ligands (entries 2–5). Compared to TBAT, several tetrabutylammonium halides such as tetrabutylammonium fluoride, -chloride, -bromide, and -iodide were tested, but they were found to be inferior (entries 6–9). Markedly, tetrabutylammonium trifluoromethanesulfonate (NBu_4OTf) did not work at all (entry 10). With regard to other fluoride sources, poor results were obtained when potassium fluoride (KF) or cesium fluoride (CsF) was employed (entries 11–12). Interestingly, in the presence of 18-crown-6, KF gave 34% of **3a** (entry 13), which might prove the importance of a naked fluoride ion. Notably, no trace of **3a** was detected with fluorotriphenysilane (entry 14) or without TBAT (entry 15), indicating that TBAT uniquely accelerated this methoxylation event (Table S1). Careful control experiments resulted in an unexpected accelerating effect on methoxylation with 30 mol % of PPh_3 (entry 1 *vs* entry 16), suggesting that an addition of PPh_3 can enhance the electrophilicity of acyl fluorides, to some extents (Table S2) [42]. It is noteworthy that the identical reaction with benzoyl chloride afforded the lower yield of **3a** (entry 17), suggesting a unique feature of acyl fluoride in this transformation.

Table 1. Optimization of the reaction conditions.



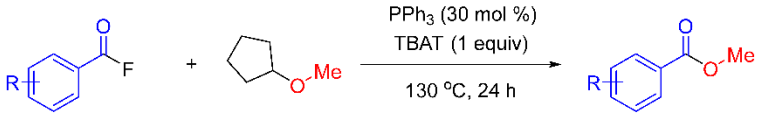
1a **2a** **3a**

Entry	[P]	Additive	Yield of 3a (%) [1]
1	PPh_3	TBAT	74 (74)
2	$P(OPh)_3$	TBAT	40

3	PCy_3	TBAT	50
4	P^tBu_3	TBAT	45
5	$P(4\text{-}F\text{-}C_6H_4)_3$	TBAT	55
6	PPh_3	NBu_4F	46
7	PPh_3	NBu_4Cl	30
8	PPh_3	NBu_4Br	14
9	PPh_3	NBu_4I	25
10	PPh_3	NBu_4OTf	0
11	PPh_3	KF	12
12	PPh_3	CsF	14
13	PPh_3	18-crown-6/KF	34
14	PPh_3	Ph_3SiF	0
15	PPh_3	-	0
16	-	TBAT	53
17[2]	PPh_3	TBAT	50

[1] Determined by gas chromatography (GC) analysis of the crude mixture using *n*-dodecane as an internal standard. An isolated yield is given in parentheses. [2] Benzoyl chloride was employed instead of **1a**.

With the optimized reaction conditions in hand, we investigated the scope and limitation of the methoxylation of an array of acyl fluorides **1** with CPME. As shown in Figure 1, this protocol displayed remarkable tolerance towards the substitution pattern and a steric effect. Both electron-donating and sterically encumbering substituents in any positions of the aryl ring gave good results. Another interesting feature of this reaction is that alkyl aryl ethers such as **3c** and **3d** were inert under the conditions. Acyl fluorides bearing electron-donating groups provided the corresponding products **3e–3g** in 64–90% isolated yields. When acyl fluorides with electron-withdrawing groups were employed, except for 4-nitrobenzoyl fluoride (**1i**), the desired products **3h**, **3j**, and **3k** were obtained in good yields. Particularly, an ester group can also be tolerated, affording the target product **3l** in 75% yield, which is noteworthy because the esters are known to be incompatible with Me_3SiI [15]. Either more sterically hindered (**3n**) or more electron-rich (**3o**) products were successfully formed in this transformation. Polyaromatic products including naphthalenes (**3p**–**3q**) and anthracene (**3r**) motifs also exhibited moderate to good levels of reactivity. Moreover, oxygen- (**3s** and **3t**), sulfur-containing heterocycles (**3u**) did not interfere toward the ester formation. To our delight, the primary and tertiary alkylated acyl fluorides also could accommodate under optimal conditions, afforded corresponding ester **3v** and **3w** in moderate yields.



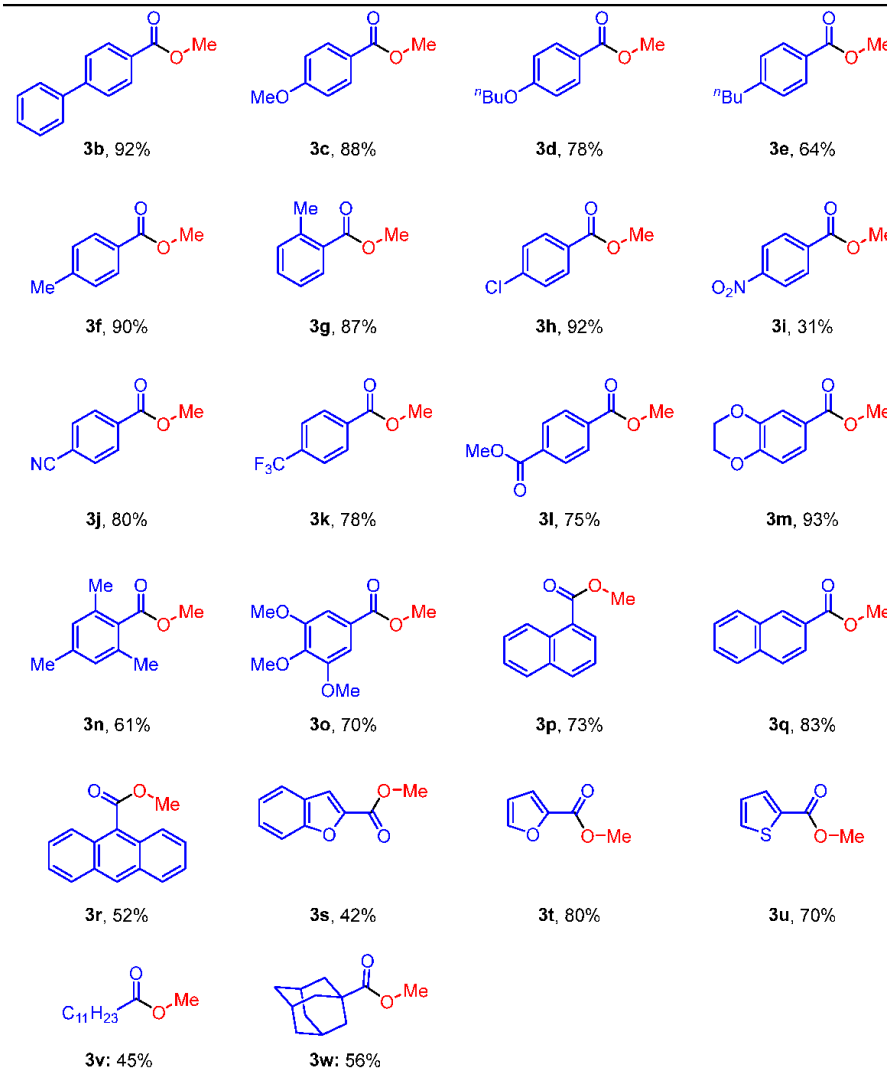
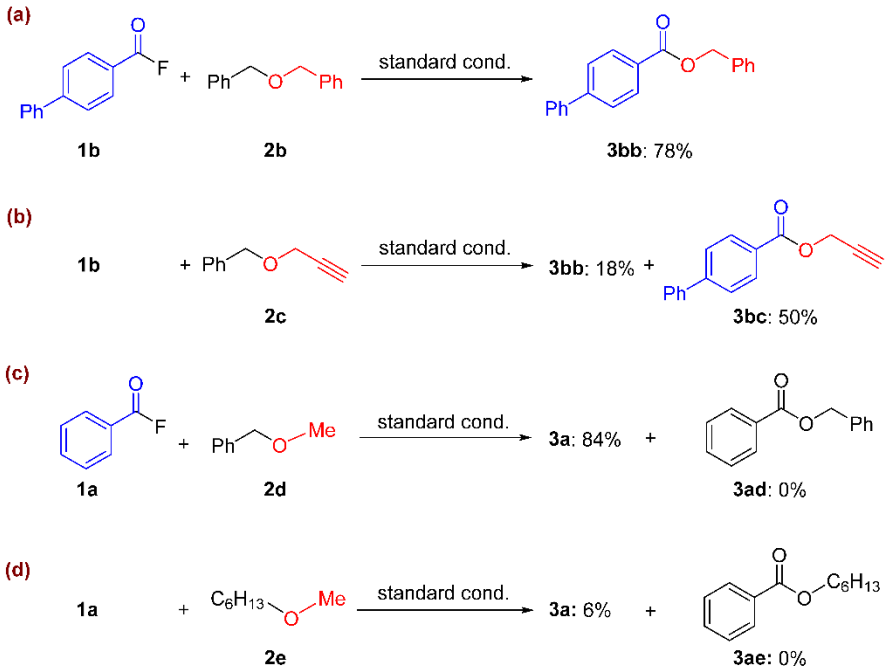


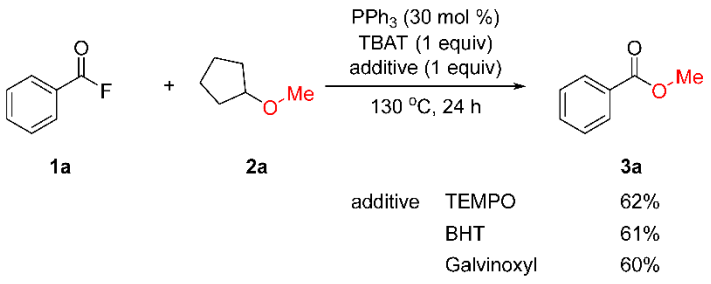
Figure 1. Methoxylation of acyl fluorides **1** with CPME (**2a**) [a,b]. [a] Reaction conditions: acyl fluorides **1** (0.2 mmol), **2a** (2 mL), PPh_3 (0.06 mmol), TBAT (0.2 mmol), 130 °C, 24 h. [b] Isolated yields.

Given a regiospecific cleavage of C–O bond in CPME, we reasoned that other ethers could also be applied in alkoxylation of acyl fluorides (Scheme 2). Dibenzyl ether (**2b**) was also a good substrate, resulting in the formation of **3bb** in 78% yield (Scheme 2a). When benzyl propargyl ether (**2c**) was employed, a propargyl group was installed preferentially into the product to afford **3bc** in 50% yield, along with 18% of **3bb** (Scheme 2b). Subsequently, unsymmetrical benzyl methyl ether (**2d**) smoothly gave **3a** in 84% yield with a high regiospecificity (Scheme 2c). In a sharp contrast, *n*-hexyl methyl ether failed to undergo the reaction, leading to only 6% of **3a** and no competitive product **3ae** was detected (Scheme 2d). Although the cleavage patterns highly depend on the reagents added [1–5], the regiospecific C–O bond cleavage in this transformation can be explained by the stability of the resulting carbocations.



Scheme 2. (**a**) Alkoxylation of **1b** with dibenzyl ether (**2b**). (**b**) Alkoxylation of acyl fluorides **1b** with benzyl propargyl ether (**2c**). (**c**) Alkoxylation of acyl fluorides **1a** with benzyl methyl ether (**2d**). (d) Alkoxylation of acyl fluorides **1a** with hexyl methyl ether (**2e**).

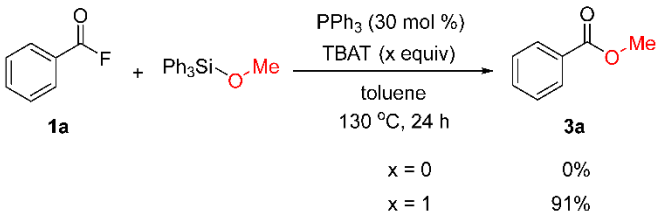
To clarify the reaction mechanism, we performed the methoxylation in the presence of radical scavengers (Scheme 3). Consequently, in the presence of equimolar amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), 2,6-di-tert-butyl-4-methylphenol (BHT), or 9,10-dihydroanthracene (DHA), the reaction proceeded with comparable efficiency to that without a radical scavenger, ruling out a radical pathway of this transformation.



Scheme 3. Methoxylation of **1a** with **2a** in the presence of radical scavengers.

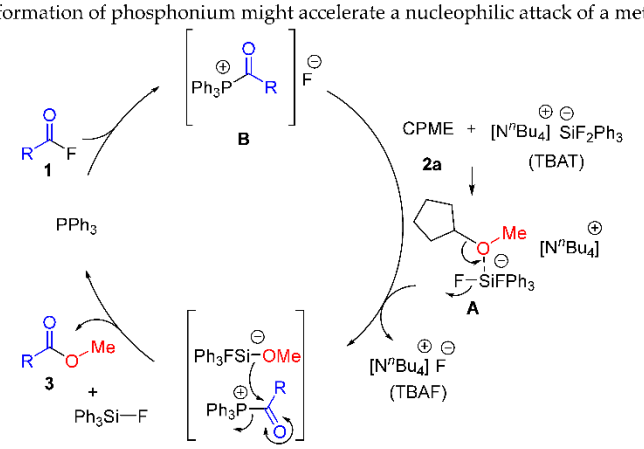
Next, we hypothesized that this PPh_3-assisted transformation might proceed via methoxytriphenylsilane (Ph_3SiOMe) as the intermediate [43]. When we carried out the reaction using Ph_3SiOMe instead of CPME under the optimized conditions (Scheme 4), no desired product **3a** was formed in the absence of TBAT, along with the recovered **1a** (91%) and Ph_3SiOMe (95%). In a sharp contrast, the reaction of **1a** with Ph_3SiOMe in the presence of TBAT, 91% of **3a** was obtained. These results indicate that the reaction of TBAT with CPME generates many nucleophilic pentacoordinate

silicates [44]. Hypervalent silicates are the key organosilicon species to promote the nucleophilic substitution step, which is normally reluctant with less nucleophilic tetracoordinate organosilicon compounds [45].



Scheme 4. Methoxylation of **1a** with Ph_3SiOMe.

A plausible reaction mechanism is outlined in Scheme 5. Initially, CPME (**2a**) interacts with TBAT to form a hypervalent silicate **A**, which is supposed to cleave C–OMe bond, affording silicate [$Ph_3FSiOMe$] . Meanwhile, acyl fluorides **1** react with PPh_3 to generate phosphonium **B** which can be more electrophilic to participate in methoxylation by nucleophilic attack of a methoxide ion to a carbonyl group, giving the desired product **3** and Ph_3SiF which was confirmed by $^{19}F\{^1H\}$ nuclear magnetic resonance (NMR) spectrum. Although a role of a catalytic amount of PPh_3 has not been clarified, the formation of phosphonium might accelerate a nucleophilic attack of a methoxide to **1**.



Scheme 5. Proposed mechanism.

3. Experimental Sections

3.1. General

Unless otherwise noted, all the reactions were carried out under an argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 °C) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using Silica gel 60 N (spherical, neutral, 40-100 µm) from Kanto Chemicals Co., Inc. (Tokyo, Japan) NMR spectra (^1H and $^{19}F\{^1H\}$) were recorded on Varian INOVA-600 (600 MHz) or Mercury-400 (400 MHz) spectrometers (Agilent Technologies International Japan, Ltd., Tokyo, Japan). Chemical shifts (δ) are in parts per million relative to $CDCl_3$ at 7.26 ppm for ^1H. The $^{19}F\{^1H\}$ NMR spectra were

measured by using CCl_3F (= 0.00 ppm) as an external standard. The NMR yields were determined using dibromomethane as an internal standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

3.2. Experimental Method

3.2.1. Representative Procedure for the Synthesis of Acyl Fluorides from Acyl Chlorides

To a 50 mL of Schlenk tube charged with a magnetic stir bar, were successively added acyl chlorides (4 mmol), 18-crown-6 (52.9 mg, 0.2 mmol, 5 mol %), KF (2.32 g, 40 mmol, 10 equivalents), and THF (20 mL). After the reaction mixture was stirred at 40 °C for 24 h, insoluble inorganic solid (KF or KCl) was filtered, and the volatiles were removed using a rotary evaporator. The crude product was purified by bulb-to-bulb distillation to afford the corresponding acyl fluorides **1** [46].

3.2.2. Representative Procedure for the Synthesis of Acyl Fluorides from Carboxylic Acids

To a 20 mL of Schlenk tube charged with a magnetic stir bar, were successively added carboxylic acids (3.0 mmol) and CH_2Cl_2 (15 mL). After the mixture was stirred at 0 °C for 30 min, Deoxo-Fluor® reagent (608 μL, 1.1 equivalents, 3.3 mmol) was slowly added to the reaction mixture. After the reaction mixture was stirred at 0 °C for 30 min, the solution was slowly poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 15 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel to afford the corresponding acyl fluorides **1** [47].

3.2.3. Synthesis of Methoxytriphenylsilane

To methanol (2 mL), were added chlorotriphenylsilane (1.179 g, 4 mmol) and triethylamine (607.1 mg, 6 mmol, 1.5 equiv). The reaction mixture was stirred under argon for 72 h until full conversion. Next, the reaction mixture was evaporated to dryness, dissolved in diethyl ether (100 mL), and washed with H_2O (1 × 5 mL, 2 × 2.5 mL). Organic phase was dried over sodium sulfate and evaporated. The crude product was purified by flash chromatography (*n*-hexane: EtOAc = 40:1) to afford methoxytriphenylsilane in 95% yield [48].

3.2.4. General Methods for the Synthesis of Benzyl Ethers **2b**–**2d**

To a solution of the corresponding alcohol (20 mmol) in DMF (20 mL), was added sodium hydride (1.2 g, 30 mmol, 60% in paraffin oil, 1.5 equivalents) at 0 °C under argon. After the reaction mixture was stirred for 30 min, benzyl bromide (2.95 mL, 30 mmol, 1.5 equivalents) was added to the reaction mixture at 0 °C and the solution was stirred at room temperature for 5 h. Then the reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (20 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica-gel column chromatography (*n*-hexane: EtOAc = 40:1) to give the corresponding benzyl ether derivatives **2b**–**2d** [49].

3.2.5. Representative Procedure for Methoxylation of Acyl Fluorides **1** with CPME (2a)

To a 20 mL Schlenk tube containing PPh_3 (15.7 mg, 0.06 mmol, 30 mol %,) and TBAT (108 mg, 0.2 mmol, 1 equivalents), were added [1,1'-biphenyl]-4-carbonyl fluoride (**1b**) (40.0 mg, 0.2 mmol,) and CPME (2.0 mL). Subsequently, the resulting mixture was heated at 130 °C. After 24 h, cyclopentyl methyl ether (**2a**) was removed by a rotary evaporator (for the high-boiling-point ethers were removed by bulb-to-bulb distillation), and the residue was purified by column chromatography (*n*-hexane: EtOAc = 20:1) to afford methyl [1,1'-biphenyl]-4-carboxylate (**3b**) (39 mg, 0.184 mmol) in 92% yield. Spectroscopic data for methyl esters matched with those previously reported in the literature, and ^1H and $^{19}F\{^1H\}$ NMR spectra of representative starting materials and the prepared products are shown in Supplementary Materials.

3.3. Characterization Data of Starting Materials and Products

Methoxytriphenylsilane [48]. Yield: 95% (1.1 g); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 7.37–7.47 (m, 9H), 7.60–7.67 (m, 6H).

((Prop-2-yn-1-yloxy)methyl)benzene (**2c**) [49]. Yield: 80% (2.34 g); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.47 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 4.62 (s, 2H), 7.29–7.33 (m, 1H), 7.34–7.39 (m, 4H).

Methyl benzoate (**3a**) [50]. Yield: 74% (20.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.42-7.47 (m, 2H), 7.53–7.58 (m, 1H), 8.02-8.07 (m, 2H).

Methyl [1,1'-biphenyl]-4-carboxylate (**3b**) [51]. Yield: 92% (39.1 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.61–7.68 (m, 4H), 8.11 (d, *J* = 8.2 Hz, 2H).

Methyl 4-methoxybenzoate (**3c**) [50]. Yield: 88% (29.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.88 (s, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H).

Methyl 4-butoxybenzoate (**3d**) [52]. Yield: 78% (32.5 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.46–1.53 (m, 2H), 1.78 (ddt, *J* = 9.1, 7.7, 6.5 Hz, 2H), 3.88 (s, 3H), 4.01 (s, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.92–8.03 (m, 2H).

Methyl 4-butylbenzoate (**3e**) [53]. Yield: 64% (24.6 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.31–1.40 (m, 2H), 1.55–1.67 (m, 2H), 2.63-2.68 (m, 2H), 3.90 (s, 3H), 7.24 (dt, *J* = 8.6, 0.6 Hz, 2H), 7.90–7.98 (m, 2H).

Methyl 4-methylbenzoate (**3f**) [50]. Yield: 90% (27.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.90 (s, 3H), 7.24 (dt, *J* = 8.0, 0.6 Hz, 2H), 7.89–7.97 (m, 2H).

Methyl 2-methylbenzoate (**3g**) [54]. Yield: 87% (26.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.89 (s, 3H), 7.22–7.26 (m, 2H), 7.39 (td, *J* = 7.5, 1.3 Hz, 1H), 7.91 (dd, *J* = 8.2, 1.2 Hz, 1H).

Methyl 4-chlorobenzoate (**3h**) [50]. Yield: 92% (31.4 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.95–8.00 (m, 2H).

Methyl 4-nitrobenzoate (**3i**) [55]. Yield: 31% (11.3 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 8.19–8.23 (m, 2H), 8.26–8.31 (m, 2H).

Methyl 4-cyanobenzoate (**3j**) [56]. Yield: 80% (25.8 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.71–7.77 (m, 2H), 8.10–8.17 (m, 2H).

Methyl 4-(trifluoromethyl)benzoate (**3k**) [50]. Yield: 78% (32.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.69–7.73 (m, 2H), 8.11–8.18 (m, 2H).

Dimethyl terephthalate (**3l**) [55]. Yield: 75% (29.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 6H), 8.10 (s, 4H).

Methyl 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate (**3m**) [57]. Yield: 93% (36.1 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.25–4.28 (m, 2H), 4.29–4.32 (m, 2H), 6.86–6.90 (m, 1H), 7.52–7.58 (m, 2H).

Methyl 2,4,6-trimethylbenzoate (**3n**) [58]. Yield: 61% (21.8 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 9H), 3.89 (s, 3H), 6.85 (s, 2H).

Methyl 3,4,5-trimethoxybenzoate (**3o**) [59]. Yield: 70% (31.7 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (d, *J* = 1.0 Hz, 12H), 7.29 (s, 2H).

Methyl 1-naphthoate (**3p**) [54]. Yield: 73% (27.2 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.48–7.56 (m, 2H), 7.62 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 7.89 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1H), 8.02 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1H), 8.19 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.89–8.95 (m, 1H).

Methyl 2-naphthoate (**3q**) [60]. Yield: 83% (31.0 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.57 (dddd, *J* = 19.6, 8.1, 6.9, 1.4 Hz, 2H), 7.88 (dt, *J* = 8.0, 1.2 Hz, 2H), 7.95 (ddt, *J* = 8.0, 1.4, 0.7 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.62 (dd, *J* = 1.6, 0.8 Hz, 1H).

Methyl anthracene-9-carboxylate (**3r**) [54]. Yield: 52% (24.6 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 3H), 7.47-7.57 (m, 4H), 8.03 (dd, *J* = 8.4, 4.1 Hz, 4H), 8.54 (s, 1H).

Methyl benzofuran-2-carboxylate (**3s**) [61]. Yield: 42% (14.8 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.31 (ddd, *J* = 7.9, 7.2, 0.8 Hz, 1H), 7.46 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.54 (t, *J* = 0.7 Hz, 1H), 7.59 (dq, *J* = 8.3, 0.8 Hz, 1H), 7.69 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H).

Methyl furan-2-carboxylate (**3t**) [62]. Yield: 80% (20.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.47 (dd, *J* = 3.5, 1.8 Hz, 1H), 7.14 (dd, *J* = 3.5, 0.9 Hz, 1H), 7.54 (dd, *J* = 1.7, 0.9 Hz, 1H).

Methyl thiophene-2-carboxylate (**3u**) [54]. Yield: 70% (20 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.55 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.80 (dd, *J* = 3.7, 1.3 Hz, 1H).

Methyl dodecanoate (**3v**) [63]. Yield: 45% (19.4 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.90 (m, 3H), 1.23–1.30 (m, 16H), 1.62 (td, *J* = 7.1, 3.0 Hz, 2H), 2.27-2.32 (m, 2H), 3.66 (s, 3H).

Methyl (3r,5r,7r)-adamantane-1-carboxylate (**3w**) [64]. Yield: 56% (21.8 mg); white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.68–1.73 (m, 6H), 1.88–1.89 (m, 6H), 1.99–2.02 (m, 3H), 3.64 (s, 3H).

Benzyl [1,1'-biphenyl]-4-carboxylate (**3bb**) [65]. Yield: 78% (45.1 mg); white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.40 (s, 2H), 7.33–7.43 (m, 4H), 7.45–7.49 (m, 4H), 7.61-7.64 (m, 2H), 7.65–7.68 (m, 2H), 8.13–8.17 (m, 2H).

Prop-2-yn-1-yl [1,1'-biphenyl]-4-carboxylate (**3bc**) [66]. Yield: 50% (23.6 mg); white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.54 (t, *J* = 2.4 Hz, 1H), 4.96 (d, *J* = 2.5 Hz, 2H), 7.39-7.43 (m, 1H), 7.45–7.50 (m, 2H), 7.61–7.64 (m, 2H), 7.66–7.70 (m, 2H), 8.12-8.18 (m, 2H).

4. Summary

In summary, we report the PPh_3-assisted methoxylation via the regiospecific cleavage of the inert C–OMe bond in CPME. This protocol demonstrated the utility of CPME as a methoxylating reagent, good functional group tolerance, and metal-free conditions. Furthermore, the regiospecific cleavage of aliphatic ethers, even in the presence of aromatic ethers, is quite difficult to achieve by conventional reagents. We believe that our study constitutes an important contribution towards a more practical use of readily available aliphatic ethers as coupling partners. Further explorations of related transformations via C–O scission are currently underway in our laboratory.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1. Details of screening the amounts of TBAT and PPh3 (Table S1), the effect of PPh_3 (Table S2), and ^{1}H and ^{19}F{^{1}H} NMR spectra of representative starting materials and final products.

Author Contributions: Z.W. developed above reactions and wrote the manuscript; Z.W. and X.W. prepared starting materials and expanded the substrates scope; Y.N. supervised the project and revised the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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Synthesis of 2-Substituted Propenes by Bidentate Phosphine-Assisted Methylenation of Acyl Fluorides and Acyl Chlorides with $AlMe_3$

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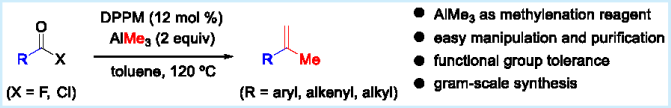
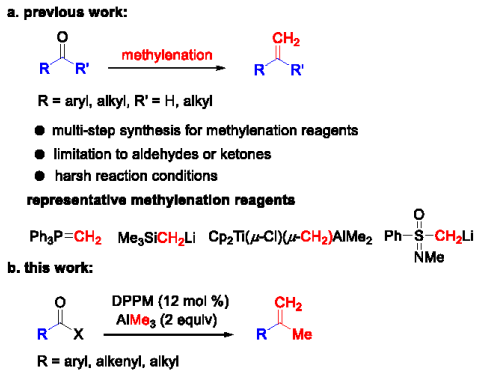
Supporting Information



ABSTRACT: Bidentate phosphine-assisted methylenation of acyl fluorides and acyl chlorides with substituted with aryl, alkenyl, and alkyl groups trimethylaluminum afforded an array of 2-substituted propene derivatives. The addition of a catalytic amount of DPPM increased an efficiency of the reactions. Trimethylaluminum as the methylenation reagent not only eliminates the presynthesis of methylene transfer reagent, but provides an efficient method for the synthesis of a series of 2-substituted propenes.

2-Substituted propenes including α-methylstyrenes are found to be prevalent in natural[1] and synthetic products,[2] as well as chiral building blocks in catalytic asymmetric processes.[3] Thus, direct and efficient synthesis of such products from the corresponding carbonyl compounds is an important class of organic transformations. Pioneering efforts on methylenation of aldehydes or ketones to the corresponding olefins have been well-documented by Wittig,[4] Johnson,[5−7] Peterson,[8] Julia,[9−11] Tebbe,[12−14] and Takai.[15] In particular, an appropriate choice of reagents is a key issue to realize methylenation procedures (Scheme 1a). Although phosphonium ylides are also well-known methylene transfer reagents, they suffered from tedious separation between triphenylphosphine oxide and the target products. In addition, the yields of target compounds were sometimes unsatisfactory, because of the low reactivity of phosphonium ylides.[6,12,14] Other representative methylenation reagents such as sulfoximine,[5] silylcarbanion,[7] sulfone,[10] and titanium−aluminum complex[12] have been studied extensively. On the other hand, late-transition-metal complexes such as Ni,[16] Cu,[17] Pd,[18] and Rh[19] have also been described to catalyze methylenation of aldehydes and ketones. However, acyl halides are still rare to be employed toward methylenation reactions, although they are inexpensive, stable, and widely abundant.[20,21] During our continuing studies on the transformation of acyl halides,[22] we discovered a simple and reliable method for the conversion of acyl halides (X = F and Cl) to 2-substituted propenes, in which trimethylaluminum acts as the methylenation reagent (Scheme 1b).

Scheme 1. Methylenation of Carbonyl Compounds



After a close look at the literature about the transformation of acyl chlorides to olefins[23] via ketones,[24] we found that one-step methylenation generating the corresponding alkenes from the corresponding carbonyl compounds is in high demand. With this consideration in mind, we commenced the study by examining the reaction of acyl chloride **1a** and 2 equiv of trimethylaluminum. Initially, the reaction was conducted in the presence of the Ni catalyst, but after extensive optimization of reaction conditions, we finally found that the nickel catalyst is not necessary (see Tables S1−S4 in the Supporting Information). Screening several additives revealed the optimized condition, as shown in Table 1. Monodentate phosphine PPh_3 afforded 59% yield of **2a**, along with the alcohol **3a** in 7% yield (Table 1, entry 1). Among bidentate

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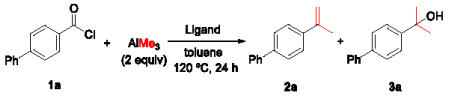
Table 1. Optimization for Methylenation of 4-Phenybenzoyl Chloride (1a) with $AlMe_3$[a]



1a 2a 3a

entry	additive	amount (mol %)	Yield[b] (%) 2a	3a
1	PPh_3	24	59	7
2	DPPM	12	93 (90)	0
3	DPPE	12	54	8
4	DPPP	12	82	18
5	DPPB	12	3	3
6	Xantphos	12	57	10
7	Et_3N	24	78	22
8	TMEDA	12	70	3
9	DPPM	2	60	0
10	DPPM	0	15	0
11[c]	DPPM	12	12	0

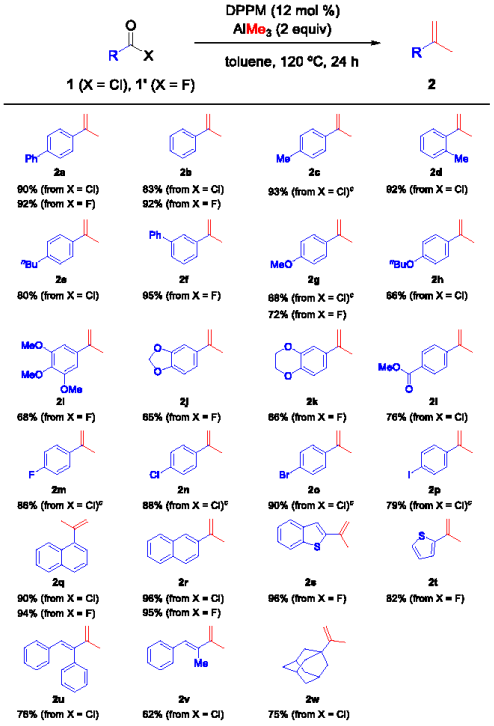
[a]Reactions were performed with **1a** (0.2 mmol), $AlMe_3$ (2 equiv), toluene (0.5 mL) at 120 °C for 24 h. [b]GC yields. An isolated yield is given in parentheses. [c]$AlMe_3$ (1 equiv) was used.

phosphines investigated (entries 2−6), DPPM showed superior results; target product **2a** was selectively delivered in 90% isolated yield (Table 1, entry 2). Meanwhile, nitrogen-containing bases such as triethylamine (Table 1, entry 7) and tetramethylethylenediamine (TMEDA; see Table 1, entry 8) also resulted in the conversion of **2a** in 78% and 70% yields, respectively. In a sharp contrast, DPPM-free reaction conditions gave only 15% yield of **2a** (Table 1, entry 10). The result shown in entry 11 suggested that 2 equiv of $AlMe_3$ are essential for complete transformation into **2a**.

With the optimized conditions of entry 2 (in Table 1) in hand, a generality for methylenation of acyl chlorides **1** or fluorides **1′** with $AlMe_3$ was examined. The results are summarized in Scheme 2. Both benzoyl chloride (**1b**) and benzoyl fluoride (**1b′**) gave **2b** in 83% and 92% yields, respectively. Acyl halides bearing alkyl and phenyl groups in various positions afforded **2c**−**2f** in good to high yields. The substrates bearing oxygen functionalities reacted smoothly to afford the corresponding products **2g**−**2k** in 65%−72% yields. Surprisingly, acyl chloride substituted by methoxycarbonyl group chemoselectively provided the target product **2l** in 76% yield. Functional compatibility of halogen-containing starting materials in this methylenation was further demonstrated. Because of the absence of any transition metals, it is noteworthy that bromide (**2o**) and iodide (**2p**) were well-tolerated. Similarly, naphthoyl chlorides and fluorides readily yielded **2q** and **2r** in good yields. Sulfur-containing heterocycles posed no problem in this transformation to give **2s** and **2t**. Strikingly, this method employing alkenylated acyl chlorides could be applied for 1,3-dienes synthesis to afford **2u** and **2v**. In addition, the reactions of tertiary aliphatic acyl chloride **1w** could readily furnished **2w** in 75% yield. In some cases, an equimolar amount of $AlMe_3$ gave rise to the formation of **2** in comparable yields obtained with 2 equiv of $AlMe_3$ addition, indicating that $AlMe_3$ play a role in two methyl-group-donating reagents.

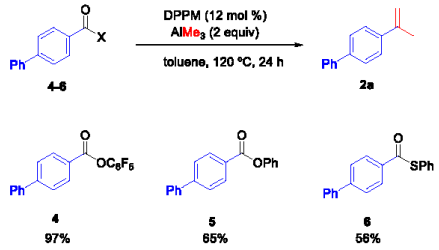
Next, a series of ester derivatives was also evaluated (Scheme 3). Perfluoro-phenolic ester **4** showed good reactivity with the aid of DPPM and afforded **2a** in 97% yield. In addition, the

Scheme 2. Scope of Acyl Halides[a,b]



[a]Reaction conditions: **1** (X = Cl) or **1′** (X = F) (0.2 mmol), $AlMe_3$ (2 equiv), DPPM (12 mol %), toluene (0.5 mL), 120 °C, 24 h. [b]Isolated yields. [c]One mmol.

Scheme 3. Scope of Carboxylic Acid Derivatives



methylenation reactions of phenolic ester **5** and thioester **6** could also undergo to give **2a** in moderate yields, which is in sharp contrast to the result for methyl ester (vide supra).

Double methylenation with 4 equiv of $AlMe_3$ was tested for the bifunctional acyl chloride **1x**. As a result, 1,4-diisopropenylbenzene (**2x**) was formed in 82% yield. In addition, with the use of phenolic ester **1y**, **2x** was delivered in 90% yield (Scheme 4a). As shown in Scheme 4b, acyl chloride **1z** with a keto group provided the unsymmetrical 1,4-methylenation product **2z**, which has been frequently used in the polymerization.[25] Otherwise, **2z** is not readily synthesized by other synthetic methods. Large-scale synthesis of 4-bromo-

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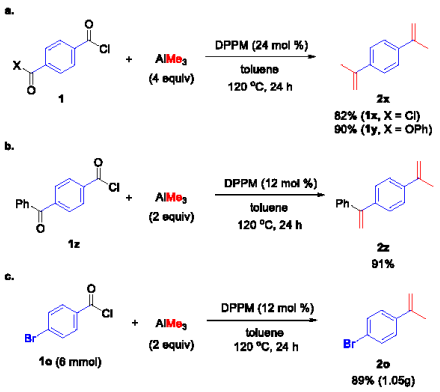
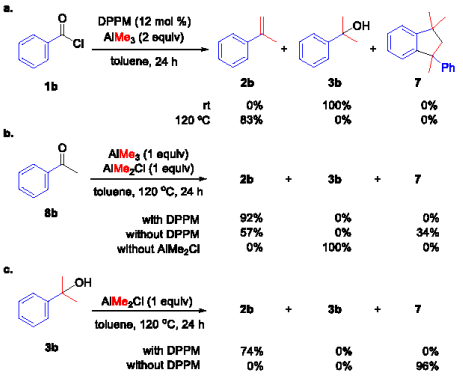
Scheme 4. Application



2-propenylbenzene (**2o**) was successful without a loss in yield (89%, 1.05 g) (Scheme 4c).

To shed light on the reaction mechanism, additional experiments were performed to prove the existence of intermediates and a role of DPPM. The reaction of **1b** with 2 equiv of $AlMe_3$ was conducted (Scheme 5a). In the reaction

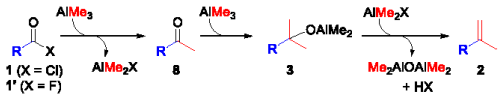
Scheme 5. Mechanistic Studies



at room temperature for 24 h, the starting material **1b** was completely consumed, along with the formation of alcohol **3b** quantitatively, but neither **2b**, nor 2,3-dihydro-1*H*-indene derivative **7**,[26] the dimerized product of **2b**, was observed. On the other hand, when the same reaction was performed at 120 °C, 83% yield of **2b** was obtained, which indicates that the high reaction temperature is important for transformation from **3b** to **2b**. The plausible intermediate acetophenone (**8b**) was subjected to the reaction with or without DPPM or $AlMe_2Cl$ (Scheme 5b). As a result, the reactions of **8b** with 1 equiv of $AlMe_3$ in the presence of 12 mol % DPPM afforded **2b** in 92% NMR yield, whereas the yield of **2b** decreased to 57% without DPPM, along with 34% of **7**. Without $AlMe_2Cl$, only alcohol **3b** was obtained with or without DPPM. This result suggests that the in-situ-formed $AlMe_2Cl$ plays an important role for transformation of **3b** to **2b**. Subsequently, the reactions of the intermediate alcohol **3b** with an equimolar amount of $AlMe_2Cl$ were elucidated (Scheme 5c). As expected, a single product **2b** was formed in 74% yield with the aid of 12 mol % of DPPM, whereas, without DPPM, byproduct **7** was obtained in 96% yield. These results are also supported with the time course of the reactions of benzoyl chloride (**1b**) or benzoyl fluoride (**1b′**) with 2 equiv of $AlMe_3$ with or without DPPM (see Figures S1 and S2 in the Supporting Information). Therefore, we concluded that the present methylenation is promoted by the in-situ-formed $AlMe_2X$ (X = F or Cl).

With the results obtained shown in Scheme 5 in hand, we propose the reaction mechanism, as shown in Scheme 6. Acyl

Scheme 6. Reaction Mechanism



halides **1** or **1′** react with the first equivalent of $AlMe_3$ to afford ketone **8**, along with the formation of $AlMe_2X$. Successively, the formed ketone **8** reacts with the second equivalent of $AlMe_3$ to form intermediate **3**.[24c] Finally, the $AlMe_2X$[27] formed in situ acts as a Lewis acid to promote the elimination of $Me_2AlOAlMe_2$, giving rise to the products **2**. Although a role of DPPM has not been clarified, the bidentate nature of DPPM might support a nucleophilic attach of $AlMe_3$ to acyl halides and tune the acidity in the catalytic system, which retards the Brønsted or Lewis acid-triggered dimerization of **2**.

In summary, we have developed a practicable, scalable, and one-step method to form 2-substituted propenes from various aryl, alkenyl, and alkyl acyl halides, as well as other esters. This protocol features good functional tolerance of halogens and chemoselectivity for esters, which would be a useful complement to other methylenation processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01059.

More-detailed results of methylenation and ^{1}H NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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Nickel-Catalyzed Decarbonylative Stannylation of Acyl Fluorides under Ligand-Free Conditions

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Abstract: Nickel-catalyzed decarbonylative stannylation of acyl fluorides under ligand-free conditions was disclosed. A variety of aromatic acyl fluorides are capable of reacting with silylstannanes in the presence of cesium fluoride. A one-pot decarbonylative stannylation/Migita-Kosugi-Stille reaction of benzoyl fluoride, giving rise to the direct formation of the corresponding cross-coupled products, further demonstrated the synthetic utility of the present method. This newly developed methodology with a good functional-group compatibility via C–F bond cleavage and C–Sn bond formation under nickel catalysis opens a new area for the functionalization of acyl fluorides in terms of carbon-heteroatom bond formation.

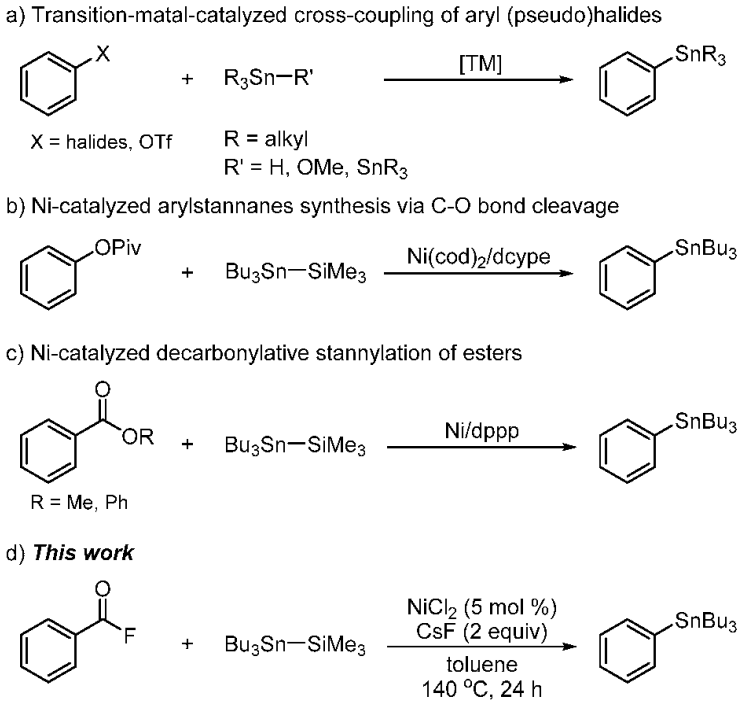
Keywords: nickel; acyl fluorides; stannylation; decarbonylation; carbon-tin bond formation

1. Introduction

Acyl fluorides as one of carboxylic acid derivatives have attracted much attention in organic synthesis, due to their great stability, easy availability, and unique intrinsic nature [1–3]. Conventionally, transition metal-catalyzed transformations of acyl fluorides with organometallic reagents (Zn, Si, and B) have focused on the synthesis of biaryl ketones in a carbonyl-group retentive manner [4–6]. In a sharp contrast, recently, decarbonylative transformations of carboxylic acid derivatives [7,8], especially acyl fluorides have been studied intensively [9]. Sakai and Ogiwara have disclosed that the auxiliary ligand of the palladium catalyst can control the reaction type of reduction of acyl fluorides [10]. However, transition-metal catalyzed decarbonylative transformations of acyl fluorides are mainly C–C bond formation, such as palladium-catalyzed trifluoromethylation [11], nickel-catalyzed Suzuki-Miyaura reaction [12], iridium-catalyzed arylation via C–H bond activation [13], and our recent work on nickel-catalyzed ethylation with BEt_3 [14] and DPPM-assisted methylenation with $AlMe_3$ [15]. Therefore, the development of carbon-heteroatom bond-forming reactions of acyl fluorides are of great importance. Very recently, we successfully demonstrated the first nickel-catalyzed decarbonylative borylation of acyl fluorides with diboron, forming the C–B bond [16], and the related decarbonylative borylation catalyzed by palladium have been reported [17,18].

Arylstannanes as one of common organometallic reagents are extensively applied in Migita-Kosugi-Stille reaction [19–21], which has been utilized as a powerful method for C–C bond formation, especially, in natural product synthesis [22–24]. Conventional synthetic methods of arylstannanes are the reactions of organometallic reagents such as arylzinc compounds with triorganotin halides [25–27]. Alternatively, catalytic cross-coupling reactions of aryl (pseudo)halides with tributyltin hydride [28], tributylstannyl methoxide [29], and hexaalkyldistannane [30,31] have been documented (Scheme 1a).

Recent studies on arylstannanes synthesis utilizing air- and moisture-insensitive silylstannyl reagent, Bu_3Sn-$SiMe_3$, could prove that the C–O bond is also a powerful alternative to aryl halides (Scheme 1b) [32]. In addition, Rueping and co-workers developed nickel-catalyzed stannylation of aromatic esters in a decarbonylative manner (Scheme 1c) [33]. Although these methods have made a great contribution to the synthesis of arylstannanes, novel and practical methods to afford arylstannanes from more simple starting materials remain highly desirable. Herein, we report the first decarbonylative stannylation of acyl fluorides with Bu_3Sn-$SiMe_3$ catalyzed by air-stable and inexpensive nickel(II) chloride under ligand and additive-free conditions (Scheme 1d).

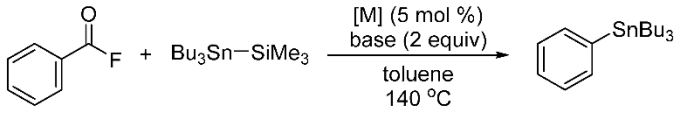


Scheme 1. Various synthetic routes for arylstannanes.

2. Results and Discussion

We commenced our research by choosing benzoyl fluoride (**1a**) and 1.5 equiv of Bu_3Sn-$SiMe_3$ (**2**) as the model substrates, and the results are summarized in Table 1. Various transition metal sources were investigated to facilitate the decarbonylative stannylation reaction (entries 1–6). Among them, nickel(II) chloride displayed a superior result, affording the target product **3a** in 90% yield (entry 3). When cesium carbonate was employed in place of cesium fluoride, the yield of **3a** was dramatically dropped to 48% (entry 7) and no stannylation reaction occurred when potassium fluoride was used, along with silylstannane **2** recovered (entry 8). Additionally, amounts of **2** could be reduced to 1.2 equiv, which afforded 94% GC yield of **3a** (entries 3, 9, and 10). The yields of **3a** were slightly decreased as the reaction time was shortened (entries 9 vs. 11–13). When benzoyl chloride was employed instead of **1a**, **3a** was obtained in 56% yield, suggesting the unique feature of the present reaction of acyl fluorides.

Table 1. Optimization of the reaction conditions.



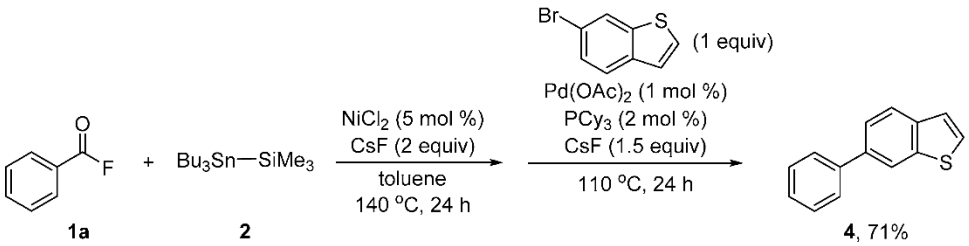
1a **2** **3a**

Entry	[M]	Base	2 (equiv)	Time (h)	Yield of 3a (%) [1]
1	$FeCl_2$	CsF	1.5	24	29
2	$CoCl_2$	CsF	1.5	24	21
3	$NiCl_2$	CsF	1.5	24	90
4	$NiBr_2$	CsF	1.5	24	68
5	$Ni(cod)_2$	CsF	1.5	24	16
6	$PdCl_2$	CsF	1.5	24	4
7	$NiCl_2$	Cs_2CO_3	1.5	24	48
8	$NiCl_2$	KF	1.5	24	0
9	$NiCl_2$	CsF	1.2	24	94 (90)
10	$NiCl_2$	CsF	1.0	24	58
11	$NiCl_2$	CsF	1.2	18	91
12	$NiCl_2$	CsF	1.2	12	87
13	$NiCl_2$	CsF	1.2	6	76

[1] Determined by GC analysis of the crude mixture using *n*-dodecane as an internal standard. An isolated yield is given in parentheses.

A generality of the decarbonylative stannylation was examined with the optimized reaction conditions (Table 2). Acyl fluorides bearing electron-donating groups such as alkyl (**1b**–**1d**), phenyl (**1e**–**1g**), and alkoxy (**1h, 1i**) groups gave the corresponding products **3b**–**3i** in 56%–85% yields regardless of the substitution positions. Other oxygen-containing functional groups such as benzyloxy (**1j**) and acetal (**1k**) were also well tolerated during the reaction. Acyl fluorides bearing electron-withdrawing groups such as trifluoromethyl (**1l**) and fluoro (**1m, 1n**) groups were also well compatible. In particular, an aryl chloride skeleton (**1o**) is known to a reactive electrophile in some nickel-catalyzed cross-coupling reactions [29]. Although 4-bromo- and 4-iodobenzoyl fluorides were employed as the substrates, no trace of the desired products was detected, presumably due to the bromo and iodo groups are highly reactive under the present reaction conditions. Acyl fluorides with fused aromatic systems (**1p**–**1r**) afforded arylstannanes in moderate to good yields. Heterocycles including benzothiophene and quinoline yielded **3s** and **3t** in 62% and 84% yields, respectively. Unfortunately, however, the reactions employing surrogate aliphatic acyl fluorides gave no formation of the desired products.

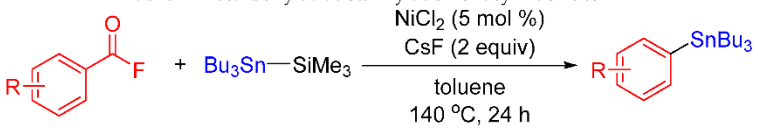
To demonstrate the synthetic utility of the present method, one-pot reaction of a successive decarbonylative stannylation/Migita-Kosugi-Stille reaction of **1a** was investigated (Scheme 2) [31]. To our delight, with the aid of the additional palladium catalyst into the reaction mixture, 71% yield of compound **4** was obtained.

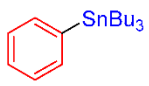
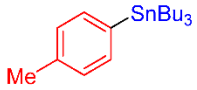
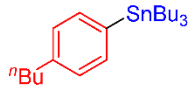
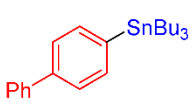
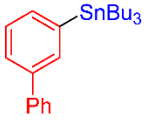
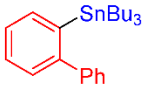
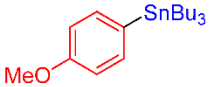
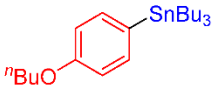
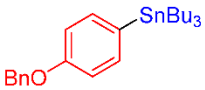
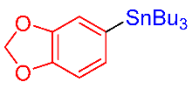
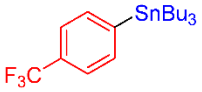
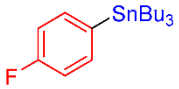
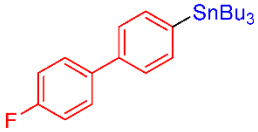
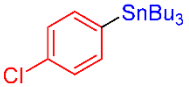
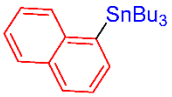
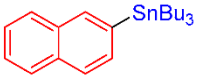
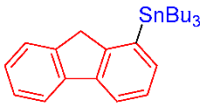
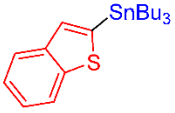
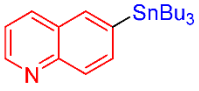


1a **2** **4**, 71%

Scheme 2. One-pot reaction of decarbonylative stannylation/Migita-Kosugi-Stille reaction of **1a**.

Table 2. Decarbonylative stannylation of acyl fluorides [a,b].

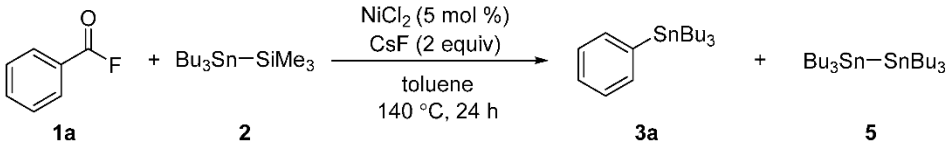


1	2		3
 **3a**, 90%	 **3b**, 81%	 **3c**, 63%	 **3d**, 67%
 **3e**, 82%	 **3f**, 56%	 **3g**, 85%	 **3h**, 64%
 **3i**, 61%	 **3j**, 50%	 **3k**, 87%	 **3l**, 61%
 **3m**, 86%	 **3n**, 72%	 **3o**, 90%	 **3p**, 51%
 **3q**, 79%	 **3r**, 82%	 **3s**, 62%	 **3t**, 84%

[a] *Reaction conditions*: **1** (0.2 mmol), **2** (0.24 mmol), $NiCl_2$ (0.01 mmol), CsF (0.4 mmol), toluene (1 mL), 140 °C, 24 h.
[b] Isolated yields.

To gain more detailed insights into the reaction mechanism, some control experiments were carried out (Table 3). Although arylstannane **3a** was obtained in 94% yield, along with the formation of hexabutylditin (**5**; 13%) under the optimized reaction conditions (entry 1), indicating that nickel(II) chloride was reduced to Ni(0) species. This hypothesis was further proved by the reaction of **1a** with **2** in the absence of cesium fluoride (entry 2). Without nickel(II) chloride, no target product **3a** was formed, and **5** was obtained quantitatively (entry 3). In some stannylation reactions, hexabutyldistannane (**5**) could also be used as a stannylating reagent [30,31]. Thus, the reaction of **1a** (0.2 mmol) with **5** (0.24 mmol) was evaluated under identical reaction conditions. However, neither the desired product **3a** nor a viable acyl stannane was delivered, along with decomposition of **1a** and the remained **5** unreacted, which suggests that the once formed **5** never be involved into the catalytic cycle because of its lower reactivity (entry 4).

Table 3. Control experiments for Ni-catalyzed decarbonylative stannylation.



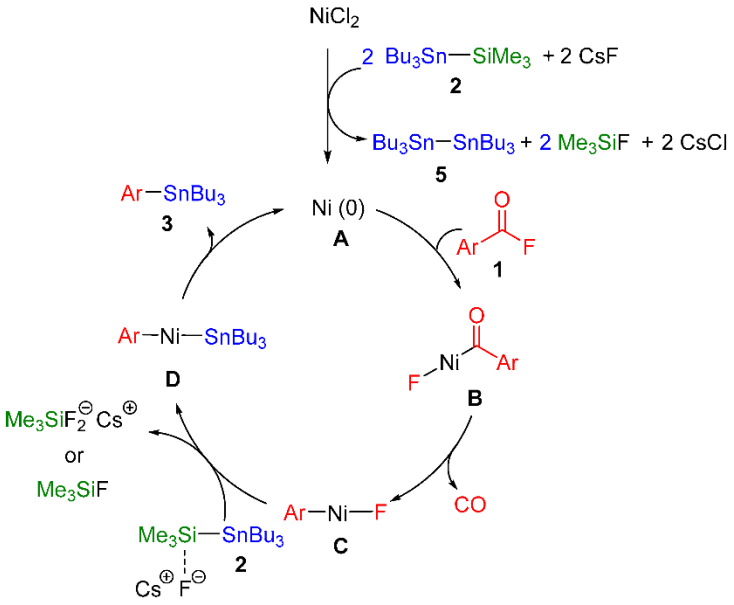
1a **2** **3a** **5**

0.2 mmol 1.2 equiv

Entry	Deviation from Standard Conditions	GC Yield (%) [1]		
		2	3a	5
1	none	0	94	13
2	without CsF	120	0	0
3	without $NiCl_2$	0	0	63
4 [2]	**5** instead of **2**	-	0	>99

[1] Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. [2] 4 (0.24 mmol) was added.

Our proposed mechanism of the present decarbonylative stannylation is outlined in Scheme 3. Combining the related references [12,34] with our previous work [16], it is assumed that oxidative addition of acyl fluorides **1** to Ni(0) species **A**, derived from reduction of Ni(II) chloride with **2**, yields acyl nickel(II) species **B**. Subsequently, decarbonylation of **B** delivers arylnickel(II) species **C** [12,16]. Transmetalation between the complex **C** and activated silylstannane **2** by cesium fluoride affords complex **D** [32]. Following reductive elimination gives the target product arylstannanes **3**, regenerating Ni(0) species **A**.



Scheme 3. Proposed mechanism.

3. Experimental Sections

3.1. General

Unless otherwise noted, all the reactions were carried out under an argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 °C) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using silica gel 60 N (spherical, neutral, 40–100 μm) from Kanto Chemicals Co., Inc. (Tokyo, Japan). NMR spectra (^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H}) were recorded on Varian INOVA-600 (600 MHz), Mercury-400 (400 MHz), or 300-NMR ASW (300 MHz) spectrometers (Agilent Technologies International Japan, Ltd., Tokyo, Japan). Chemical shifts (δ) are in parts per million relative to $CDCl_3$ at 7.26 ppm for ^{1}H and at 77.16 ppm for ^{13}C{^{1}H}. The ^{19}F{^{1}H} NMR spectra were measured by using CCl_3F (δ= 0.00 ppm) as an external standard. The NMR yields were determined using dibromomethane as an internal standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. GC analyses were performed on a Shimadzu GC-14A equipped with a flame ionization detector using Shimadzu Capillary Column (CBP1-M25-025) and Shimadzu C-R6A-Chromatopac integrator (Kyoto, Japan). Infrared spectra were recorded on a SHIMADZU IRPrestige-21 spectrophotometer. Elemental analyses were carried out with a Perkin-Elmer 2400 CHN elemental analyzer (Perkin-Elmer, Waltham, MA, USA) at Okayama University. ^{1}H NMR, ^{13}C{^{1}H} NMR, ^{19}F{^{1}H} NMR spectra of the compounds **1t**, **2**, **3a**–**t** and **4** can be found at the Supplementary Materials.

3.2. Experimental Method

3.2.1. Representative Procedure for the Synthesis of Acyl Fluorides from Acyl Chlorides

To a 50 mL of Schlenk tube charged with a magnetic stir bar, were successively added acyl chloride (4.0 mmol), 18-crown-6 (52.9 mg, 0.2 mmol, 5 mol %), KF (2.32 g, 40 mmol, 10 equiv), and THF (20 mL). After the reaction was stirred at 40 °C for 24 h, insoluble inorganic solid (KF or KCl) was filtered, and the volatiles were concentrated using a rotary evaporator. The crude product was purified by bulb-to-bulb distillation to afford the corresponding acyl fluorides **1** [35].

3.2.2. Representative Procedure for the Synthesis of Acyl Fluorides from Carboxylic Acids

To a 20 mL of Schlenk tube charged with a magnetic stir bar, were successively added carboxylic acid (3.0 mmol) and CH_2Cl_2 (15 mL). After the mixture was stirred at 0 °C for 30 min, Deoxo-Fluor® reagent (608 μL, 3.3 mmol, 1.1 equiv) was slowly added to the reaction mixture. After the reaction mixture was stirred at 0 °C for 30 min, the solution was slowly poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 15 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel to afford the corresponding acyl fluorides **1** [36].

3.2.3. Synthesis of Trimethyl(tributylstannyl)silane (**2**)

To a solution of naphthalene (51.3 mg, 0.4 mmol) in THF (16 mL), was added lithium clippings (84 mg, 12 mmol) under an argon atmosphere. During the resulting mixture was stirred at room temperature for 1 h, the color turned to dark green. Then, hexabutylditin (2.02 mL, 4 mmol) was added dropwise and the mixture was stirred at room temperature for 3 h. The resulting solution (16 mL) was transferred via cannula to a Schlenk tube under Ar and then stored at room temperature. A THF solution prepared as described above was added via a cannula into the stirred solution of chlorotrimethylsilane (951 mg, 8.8 mmol) in THF at 0 °C. The reaction was stirred at room temperature overnight followed by extraction with hexane. The organic phase was washed with brine and dried

over Na_2SO_4. Removal of the solvent and purification by bulb-to-bulb distillation under reduced pressure provided Bu_3Sn-$SiMe_3$ as a colorless oil [37].

3.2.4. Representative Procedure for Ni-catalyzed Decarbonylative Stannylation of Acyl Fluorides

A 20 mL dried Schlenk tube containing a stirring bar and CsF (60.8 mg, 0.4 mmol, 2 equiv) was dried with a heat gun under reduced pressure and filled with Ar after cooling to room temperature. To this vessel, were added $NiCl_2$ (1.3 mg, 0.01 mmol, 5 mol %), toluene (1 mL), acyl fluorides (**1**) (0.2 mmol, 1 equiv) and trimethyl(tributylstannyl)silane (**2**) (87.2 mg, 0.24 mmol, 1.2 equiv). The mixture was heated at 140 °C with stirring for 24 h. The solution was then cooled to room temperature, and the solvent was removed under vacuum. The decarbonylative stannylation products **3** were purified by flash column chromatography on silica gel.

3.2.5. One-Pot Decarbonylative Stannylation/Migita-Kosugi-Stille Cross-Coupling Reaction of **1a**

A 20 mL dried Schlenk tube containing a stirring bar and CsF (60.8 mg, 0.4 mmol, 2 equiv) was dried with a heat gun under reduced pressure and filled with Ar after cooling to room temperature. To this vessel, were added with $NiCl_2$ (1.3 mg, 0.01 mmol, 5 mol %), toluene (1 mL), benzoyl fluoride (**1a**) (24.8 mg, 0.2 mmol), and trimethyl(tributylstannyl)silane (**2**) (87.2 mg, 0.24 mmol, 1.2 equiv). The mixture was heated at 140 °C with stirring for 24 h. The solution was then cooled to room temperature. 6-Bromobenzo[*b*]thiophene (42.6 mg, 0.2 mmol, 1 equiv), palladium acetate (0.4 mg, 0.002 mmol, 1 mol %), tricyclohexylphosphine (1.1 mg, 0.004 mmol, 2 mol %), and anhydrous cesium fluoride (45.6 mg, 0.3 mmol, 1.5 equiv) were added to the reaction mixture. The mixture was heated at 110 °C with stirring. After 24 h, the reaction mixture was cooled, the volatiles were evaporated under reduced pressure. The product was purified by flash chromatography on silica gel by elution with hexane, compound **4** was obtained in 71% yield (30 mg, 0.14 mmol) as white solid [31].

3.3. Characterization Data of Starting Materials and Products

Quinoline-6-carbonyl fluoride (**1t**). Yield: 55% (288.8 mg); white solid; melting point: 104–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.56 (m, 1H), 8.20–8.25 (m, 2H), 8.30 (dd, J = 8.4, 1.9 Hz, 1H), 8.62 (d, J = 1.9 Hz, 1H), 9.08 (dd, J = 4.3, 1.9 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 122.5, 123.1, 127.4, 129.4 (d, $J_{C\text{-}F}$ = 4.0 Hz), 130.8 (d, $J_{C\text{-}F}$ = 1.4 Hz), 133.9 (d, $J_{C\text{-}F}$ = 3.0 Hz), 137.6, 150.7, 153.8, 156.9 (d, $J_{C\text{-}F}$ = 344.2 Hz); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ 18.9; FT-IR (neat, cm^{-1}): 735 (s), 781 (s), 854 (s), 1011 (s), 1045 (s), 1171 (s), 1231 (s), 1622 (s), 1805 (s); Anal. Calcd for $C_{14}H_9FO_3$: C, 68.57; H, 3.45; N, 8.00%. Found: C, 68.50; H, 3.23; N, 7.95%.

Trimethyl(tributylstannyl)silane (**2**) [37]. Yield: 92% (2.67 g); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.23 (s, $J_{H\text{-}Sn}$ = 26.4 Hz, 9H), 0.84–0.90 (m, 15H), 1.29 (sext, J = 7.3 Hz, 6H), 1.44–1.48 (m, 6H).

Tributyl(phenyl)stannane (**3a**) [33]. Yield: 90% (66.1 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91–0.95 (m, 9H), 1.03–1.16 (m, $J_{H\text{-}Sn}$ = 54.6 Hz, 6H), 1.33–1.41 (m, 6H), 1.53–1.63 (m, 6H), 7.32–7.36 (m, 3H), 7.46–7.54 (m, $J_{H\text{-}Sn}$ = 36.4 Hz, 2H).

Tributyl(p-tolyl)stannane (**3b**) [33]. Yield: 81% (61.8 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.00–1.10 (m, $J_{H\text{-}Sn}$ = 52.4 Hz, 6H), 1.31–1.38 (m, 6H), 1.48–1.59 (m, 6H), 2.35 (s, 3H), 7.17 (d, J = 7.2 Hz, 2H), 7.37 (d, J = 7.8 Hz, $J_{H\text{-}Sn}$ = 35.8 Hz, 2H).

Tributyl(o-tolyl)stannane (**3c**) [31]. Yield: 63% (48.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.01–1.14 (m, $J_{H\text{-}Sn}$ = 50.4 Hz, 6H), 1.34 (sext, J = 7.2 Hz, 6H), 1.47–1.58 (m, 6H), 2.40 (s, 3H), 7.12–7.17 (m, 1H), 7.17–7.25 (m, 2H), 7.40 (d, J = 6.8 Hz, $J_{H\text{-}Sn}$ = 42.8 Hz, 1H).

Tributyl(4-butylphenyl)stannane (**3d**). Yield: 67% (56.7 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.6 Hz, 9H), 0.94 (t, J = 7.6 Hz, 3H), 0.99–1.12 (m, $J_{H\text{-}Sn}$ = 50.8 Hz, 6H), 1.29–1.40 (m, 8H), 1.50–1.64 (m, 8H), 2.60 (t, J = 7.8 Hz, 2H), 7.14–7.19 (m, 2H), 7.37 (d, J = 6.4 Hz, $J_{H\text{-}Sn}$ = 39.2 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 9.7 ($J_{C\text{-}Sn}$ = 338.7 Hz), 13.8, 14.1, 22.6, 27.6 ($J_{C\text{-}Sn}$ = 57.2 Hz), 29.3

($J_{C\text{-}Sn}$ = 19.8 Hz), 33.8, 35.8, 128.3 ($J_{C\text{-}Sn}$ = 41.2 Hz), 136.5 ($J_{C\text{-}Sn}$ = 31.3 Hz), 138.3, 142.7; FT-IR (neat, cm^{-1}): 729 (m), 748 (m), 1070 (m), 1045 (m), 1377 (m), 1458 (m), 2855 (m), 2872 (m), 2928 (m), 2959 (m); Anal. Calcd for $C_{22}H_{40}Sn$: C, 62.43; H, 9.53%. Found: C, 62.30; H, 9.55%.

[1,1′-Biphenyl]-4-yltributylstannane (**3e**) [33]. Yield: 82% (72.7 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 9H), 1.03–1.18 (m, $J_{H\text{-}Sn}$ = 43.2 Hz, 6H), 1.38 (sext, J = 7.5 Hz, 6H), 1.55–1.66 (m, 6H), 7.35–7.39 (m, 1H), 7.45–7.48 (m, 2H), 7.53–7.60 (m, 4H), 7.62–7.64 (m, 2H).

[1,1′-Biphenyl]-3-yltributylstannane (**3f**) [33]. Yield: 56% (49.6 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 9H), 1.06–1.16 (m, $J_{H\text{-}Sn}$ = 50.8 Hz, 6H), 1.33–1.38 (m, 6H), 1.54–1.63 (m, 6H), 7.35–7.38 (m, 1H), 7.40–7.48 (m, 4H), 7.51–7.54 (m, 1H), 7.58–7.62 (m, 2H), 7.63–7.71 (d, J = 1.8 Hz, $J_{H\text{-}Sn}$ = 40.2 Hz, 1H).

[1,1′-Biphenyl]-2-yltributylstannane (**3g**) [33]. Yield: 85% (75.4 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.69–0.77 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 0.84 (t, J = 7.3 Hz, 9H), 1.23 (sext, J = 7.8 Hz, 6H), 1.32–1.38 (m, 6H), 7.32–7.35 (m, 3H), 7.36–7.39 (m, 3H), 7.39–7.42 (m, 2H), 7.56 (d, J = 7.3 Hz, $J_{H\text{-}Sn}$ = 40.8 Hz, 1H).

Tributyl(4-methoxyphenyl)stannane (**3h**) [31]. Yield: 64% (50.8 mg); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 9H), 0.96–1.09 (m, $J_{H\text{-}Sn}$ = 51.2 Hz, 6H), 1.33 (sext, J = 7.6 Hz, 6H), 1.48–1.59 (m, 6H), 3.81 (s, 3H), 6.91 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, $J_{H\text{-}Sn}$ = 37.2 Hz, 2H).

(4-Butoxyphenyl)tributylstannane (**3i**). Yield: 61% (53.6 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 9H), 0.98 (t, J = 7.2 Hz, 3H), 1.01–1.04 (m, $J_{H\text{-}Sn}$ = 51.6 Hz, 6H), 1.33 (sext, J = 7.8 Hz, 6H), 1.47–1.58 (m, 8H), 1.75–1.80 (m, 2H), 3.96 (t, J = 6.6 Hz, 2H), 6.90 (d, J = 8.5 Hz, $J_{H\text{-}Sn}$ = 61.8 Hz, 2H), 7.36 (d, J = 8.5 Hz, $J_{H\text{-}Sn}$ = 42.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 9.7 ($J_{C\text{-}Sn}$ = 333.0 Hz), 13.9, 14.0, 19.4, 27.6 ($J_{C\text{-}Sn}$ = 55.5 Hz), 29.2 ($J_{C\text{-}Sn}$ = 20.8 Hz), 31.5, 67.4, 114.6 ($J_{C\text{-}Sn}$ = 43.9 Hz), 131.8, 137.6 ($J_{C\text{-}Sn}$ = 34.7 Hz), 159.4; FT-IR (neat, cm^{-1}): 671 (m), 754 (m), 1072 (m), 1130 (m), 1207 (m), 1242 (m), 1273 (m), 1464 (m), 1495 (m), 1585 (m), 2855 (m), 2872 (m), 2928 (m), 2959 (m); Anal. Calcd for $C_{22}H_{40}OSn$: C, 60.15; H, 9.18%. Found: C, 60.09; H, 9.32%.

(4-(Benzyloxy)phenyl)tributylstannane (**3j**) [38]. Yield: 50% (47.3 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 0.98–1.10 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.34 (sext, J = 7.2 Hz, 6H), 1.52–1.57 (m, 6H), 5.07 (s, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.32–7.36 (m, 1H), 7.37–7.43 (m, 4H), 7.46 (d, J = 7.2 Hz, 2H).

Benzo[d][1,3]dioxol-5-yltributylstannane (**3k**) [29]. Yield: 87% (71.5 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 0.99–1.08 (m, $J_{H\text{-}Sn}$ = 49.8 Hz, 6H), 1.33 (sext, J = 7.8 Hz, 6H), 1.50–1.58 (m, 6H), 5.92 (s, 2H), 6.86 (d, J = 7.4 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.94 (s, $J_{H\text{-}Sn}$ = 37.2 Hz, 1H).

Tributyl(4-(trifluoromethyl)phenyl)stannane (**3l**) [33]. Yield: 61% (53.1 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.89 (m, J = 7.2 Hz, 9H), 1.04–1.15 (m, $J_{H\text{-}Sn}$ = 50.6 Hz, 6H), 1.33 (sext, J = 7.2 Hz, 6H), 1.50–1.57 (m, 6H), 7.55 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, $J_{H\text{-}Sn}$ = 34.8 Hz, 2H).

Tributyl(4-fluorophenyl)stannane (**3m**) [33]. Yield: 86% (66.2 mg); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 9H), 0.98–1.12 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.33 (sext, J = 8.0 Hz, 6H), 1.47–1.60 (m, 6H), 7.00–7.08 (m, 2H), 7.35–7.48 (m, 2H).

Tributyl(4′-fluoro-[1,1′-biphenyl]-4-yl)stannane (**3n**) [33]. Yield: 72% (66.4 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 9H), 1.05–1.15 (m, $J_{H\text{-}Sn}$ = 50.1 Hz, 6H), 1.36 (sext, J = 7.2 Hz, 6H), 1.54–1.62 (m, 6H), 7.13 (dd, J = 8.7 Hz, $J_{F\text{-}H}$ = 8.7 Hz, 2H), 7.51–7.53 (m, 2H), 7.54–7.57 (m, 4H).

Tributyl(4-chlorophenyl)stannane (**3o**) [37]. Yield: 90% (72.3 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 9H), 1.00–1.10 (m, $J_{H\text{-}Sn}$ = 50.1 Hz, 6H), 1.32 (sext, J = 7.2 Hz, 6H), 1.47–1.56 (m, 6H), 7.28–7.33 (m, 2H), 7.34–7.42 (m, $J_{H\text{-}Sn}$ = 36.0 Hz, 2H).

Tributyl(naphthalen-1-yl)stannane (**3p**) [33]. Yield: 51% (42.6 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 9H), 1.19–1.22 (m, $J_{H\text{-}Sn}$ = 50.4 Hz, 6H), 1.35 (sext, J = 7.8 Hz, 6H), 1.54–1.60

(m, 6H), 7.42–7.51 (m, 3H), 7.63 (d, J = 6.6 Hz, $J_{H\text{-}Sn}$ = 46.2 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H).

Tributyl(naphthalen-2-yl)stannane (**3q**) [33]. Yield: 79% (65.9 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (m, J = 7.2 Hz, 9H), 1.09–1.21 (m, $J_{H\text{-}Sn}$ = 50.1 Hz, 6H), 1.38 (sext, J = 7.2 Hz, 6H), 1.56–1.65 (m, 6H), 7.44–7.51 (m, 2H), 7.59 (d, J = 8.1 Hz, $J_{H\text{-}Sn}$ = 33.0 Hz, 1H), 7.79–7.87 (m, 3H), 7.96 (s, $J_{H\text{-}Sn}$ = 44.4 Hz, 1H).

Tributyl(9H-fluoren-1-yl)stannane (**3r**). Yield: 82% (74.7 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.11–1.23 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.36 (sext, J = 7.2 Hz, 6H), 1.52–1.62 (m, 6H), 3.85 (s, 2H), 7.30–7.42 (m, 4H), 7.57 (d, J = 7.5 Hz, 1H), 7.76 (dd, J = 7.2, 1.2 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 9.8 ($J_{C\text{-}Sn}$ = 338.7 Hz), 13.8, 27.6 ($J_{C\text{-}Sn}$ = 60.1 Hz), 29.4 ($J_{C\text{-}Sn}$ = 19.6 Hz), 39.4, 119.9, 120.0, 125.0, 126.3, 126.6, 126.9, 135.0, 138.3, 140.3, 142.2, 143.0, 150.8; FT-IR (neat, cm^{-1}): 731 (m), 752 (m), 1207 (s), 1220 (m), 1225 (m), 1456 (m), 1464 (m), 1695 (m), 2855 (m), 2865 (m), 2926 (m), 2959 (m); Anal. Calcd for $C_{25}H_{36}Sn$: C, 65.95; H, 7.97%. Found: C, 66.06; H, 8.20%.

Benzo[b]thiophen-2-yltributylstannane (**3s**) [39]. Yield: 62% (52.5 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 9H), 1.12–1.20 (m, $J_{H\text{-}Sn}$ = 52.2 Hz, 6H), 1.36 (sext, J = 7.2 Hz, 6H), 1.56–1.64 (m, 6H), 7.27–7.29 (m, 1H), 7.32 (t, J = 6.6 Hz, 1H), 7.39 (s, $J_{H\text{-}Sn}$ = 24.0 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H).

6-(Tributylstannyl)quinoline (**3t**) [32]. Yield: 84% (70.3 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 9H), 1.08–1.20 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.36 (sext, J = 7.8 Hz, 6H), 1.53–1.64 (m, 6H), 7.39 (dd, J = 8.4, 4.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, $J_{H\text{-}Sn}$ = 31.5 Hz, 1H), 7.91 (s, $J_{H\text{-}Sn}$ = 42.0 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.89 (dd, J = 8.4, 1.2 Hz, 1H).

6-Phenylbenzo[b]thiophene (**4**) [40]. Yield: 71% (30.0 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.42 (m, 2H), 7.46–7.51 (m, 3H), 7.61 (dd, J = 8.4, 1.8 Hz, 1H), 7.66–7.90 (m, 2H), 7.95 (d, J = 8.4, 1H), 8.04 (d, J = 1.8 Hz, 1H).

4. Summary

In summary, we have developed an efficient and convenient method for the inexpensive $NiCl_2$-catalyzed decarbonylative stannylation of a series of acyl fluorides, which is notable for being both ligand and additive-free. A one-pot decarbonylative stannylation/Migita-Kosugi-Stille reaction further demonstrated the synthetic applicability of our protocol because the isolation of toxic organotin compounds is not necessary. This study can expand the chemistry of acyl fluorides in terms of carbon-heteroatom bond formations.

Supplementary Materials: The following are available online. ^{1}H NMR, ^{13}C{^{1}H} NMR, ^{19}F{^{1}H} NMR spectra of representative starting materials and final products.

Author Contributions: X.W. developed above reactions and wrote the manuscript; X.W., Z.W. and L.L. prepared starting materials and expanded the substrates scope; Y.A. conducted the additional experiments required by reviewers; Y.N. supervised the project and revised the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **3a**–**3t** are available from the authors.

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Nickel/copper-cocatalyzed decarbonylative silylation of acyl fluorides†

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Ni/Cu-cocatalyzed decarbonylative silylation of acyl fluorides with silylboranes has been developed to afford various arylsilanes with high efficiency and good functional-group compatibility *via* carbon–fluorine bond cleavage and carbon–silicon bond formation. Such transformation can not only extend the functionalization type of acyl fluorides but complement the synthetic route for arylsilanes.

Since organosilicon compounds are of great importance in organic synthesis,[1] drug discovery[2] and materials science,[3] various synthetic strategies have been established by constructing the C–Si bond. Traditional synthetic methods of arylsilanes involve the reactions of Grignard or organolithium reagents with silyl electrophiles,[1a,4] in which ester and ketone functional groups cannot be incorporated. Alternatively, transition-metal-catalyzed silylation of aryl halides has been developed for the preparation of arylsilanes.[5] Although defluorosilylation of fluoroarenes *via* C–F bond activation has been reported recently, the synthesis of the starting materials requires multi-step reactions.[6]

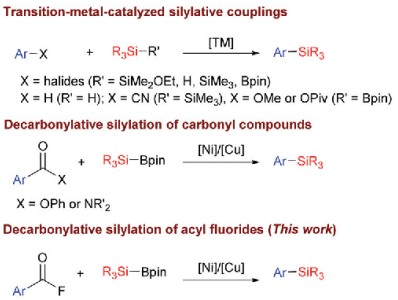
In addition, a direct C–H silylation of unreactive aromatic compounds with hydrosilanes was also investigated to obtain arylsilanes.[7] Furthermore, silylation of nitriles with disilanes *via* C–CN bond cleavage[8] and of pivalates or anisoles with silylboranes *via* C–O bond cleavage[9] provided a new access to arylsilanes (Scheme 1a).

Utilizing decarboxylation/decarbonylation, transformations of carboxylic acid and their derivatives into valuable compounds under transition metal catalysis have drawn much attention owing to their natural abundance and easy availability.[10] Among them, an early study found that palladium-catalyzed silylation of acyl chlorides bearing strong electron-withdrawing groups with hexamethyldisilanes gave a mixture of acylsilane and arylsilane, in which the selective decarbonylative silylation of acyl chlorides was observed with chlorinated disilanes.[11]

Rueping[12] and Shi[13] independently succeeded in nickel/copper-cocatalyzed decarbonylative silylation of phenolic esters *via* C–O bond cleavage. Building upon the previous work, Reuping expanded the decarbonylation silylation strategy for arylamides *via* C–N bond cleavage (Scheme 1b).[14] However, phenolic esters and arylamides are generally prepared from the corresponding carboxylic acids *via* acyl chlorides in two steps, and a large amount of waste derived from phenols and amines is generated after the reaction.[12,14]

On the other hand, acyl fluorides display much superiority over the corresponding carboxylic derivatives, showing great stability and high reactivity.[15] Moreover, acyl fluorides acting as the acyl fragment without a CO loss in transition-metal-catalyzed transformations have been witnessed in cross-couplings of Negishi,[16] Hiyama,[17] Suzuki–Miyaura,[18] and other reactions such as reductive coupling with vinyl triflates,[19] reduction,[20] boroacylation of allenes,[21] and C–H coupling with azoles[22] to give the corresponding ketones or aldehydes.

Recently, reactions of acyl fluorides serving as an arylation moiety *via* a decarbonylative process for C–C bond formation have



Scheme 1 Synthetic routes for arylsilanes.

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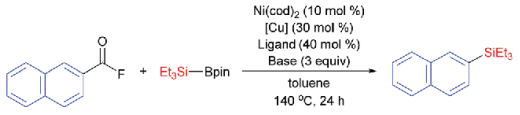
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of ^{1}H, $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra. See DOI: 10.1039/c9cc05325e

been extensively investigated, including trifluoromethylation,[23] reduction,[20b] Suzuki–Miyaura type-arylation,[24] and direct C–H arylation.[25] We have also reported the $Ni(cod)_2$/DPPE catalytic system for decarbonylative alkylation of acyl fluorides.[26] The outcome suggested that utilization of acyl fluoride is the key to this transformation and other acyl halides cannot be participated.

Due to the indispensable and versatile main group elements, namely, boron, silicon, and tin in cross-coupling chemistry,[27] carbon–heteroatom bond-forming reactions of acyl fluorides are highly desired. Encouraged by the unique nature of acyl fluorides in various decarbonylative C–C bond-forming reactions and our continuous interest in acyl halides in cross-coupling reactions,[26,28] we have developed nickel-catalyzed borylation[29] and stannylation[30] of acyl fluorides with diborons and silylstannanes, respectively, in a decarbonylation manner. Herein, we report our new approach to the synthesis of arylsilanes by nickel/copper-cocatalyzed decarbonylative silylation of acyl fluorides with silylboranes (Scheme 1c).

Initially, we chose the reaction of 2-naphthoyl fluoride (**1a**) with silylborane **2a** under basic conditions as the model reaction. An inexpensive PPh_3 ligand was preferable due to its excellent performance in nickel-catalyzed decarbonylative borylation.[29] However, only 5% of silylated product **3a** was detected, along with a large amount of unconsumed **2a** (Table 1, entry 1), where 22% of naphthalene from decarbonylative reduction and 58% of 2,2′-binaphthalene derived from decarbonylative homocoupling were observed. This outcome revealed that the nickel/PPh_3 catalytic system cannot efficiently activate **2a** to promote transmetalation of the oxidative adduct. Thus, CuOAc was added because of the reported profound effect of copper salts in activation of the Si–B bond.[31] As expected, 85% of **3a** was obtained, along with 10% of naphthalene as a by-product (entry 2). Notably, cooperation of the copper salt suppressed the competitive decarbonylative homocoupling and reduction.

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

Entry	[Cu]	Ligand	Base	3a[b] (%)
1	—	PPh_3	KF	5
2	CuOAc	PPh_3	KF	85
3	CuOAc	PCy_3	KF	50
4	CuOAc	P^nBu_3	KF	32
5	CuOAc	$P(OPh)_3$	KF	11
6	CuOAc	PPh_3	CsF	18
7	CuOAc	PPh_3	NaF	49
8	CuOAc	PPh_3	LiF	45
9	CuOAc	PPh_3	KOAc	71
10	$Cu(OAc)_2$	PPh_3	KF	31
11	$CuCl_2$	PPh_3	KF	0
12	CuF_2	PPh_3	KF	77
13[c]	CuF_2	PPh_3	KF	89 (85)
14[d]	CuF_2	PPh_3	KF	0
15	CuF_2	—	KF	<1
16	CuF_2	PPh_3	—	46
17[e]	CuF_2	PPh_3	KF	0

[a] **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol) in toluene (1.0 mL) at 140 °C for 24 h. [b] Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. The isolated yield is given in parentheses. [c] 150 °C. [d] Without $Ni(cod)_2$. [e] 2-Naphthoyl chloride instead of **1a**.

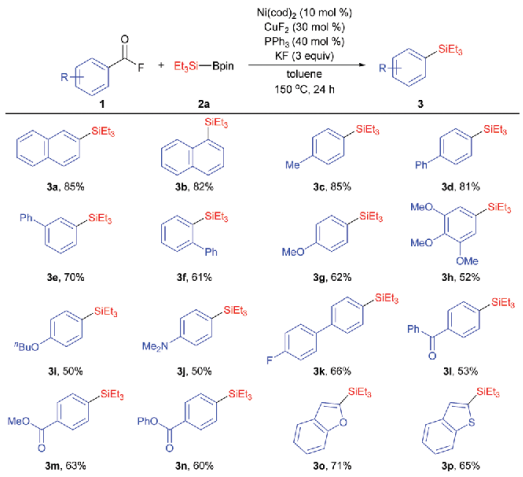
Other monodentate phosphine ligands such as PCy_3, P^nBu_3, and $P(OPh)_3$ showed moderate to poor activities in this transformation (entries 3–5). Although acyl fluorides could act as a mild base in some cases,[24] an exogenous base is still required in the present silylation reaction. Among the bases used, KF gave the best result (entry 2 and entries 6–9). Various cuprous and cupric salts were also examined (entries 10–13 and Table S5, ESI†), and CuF_2 showed a superior result with the target product **3a** in 89% yield (entry 13). Screening of the reaction temperatures demonstrated that a higher reaction temperature greatly increased the conversion of **1a** to the decarbonylative silylation product **3a**, suppressing the formation of the homocoupled product (Table S6, ESI†). Control experiments shown in entries 14 and 15 confirmed the crucial factors of $Ni(cod)_2$ and PPh_3 to succeed in this transformation; no or a trace of **3a** was observed. In the absence of KF, only 46% formation of **3a** was detected (entry 16). In sharp contrast, upon employing 2-naphthoyl chloride instead of **1a** under the optimized reaction conditions, **2a** remained unreacted and no silylation product **3a** was formed (entry 17). We reasoned that the oxidative adduct $NiAr(Cl)(PPh_3)_2$ cannot undergo ligand exchange with silylboranes.[24] This different reactivity demonstrated the unique nature of acyl fluorides in the present silylation. It is noteworthy that no acylsilane in a retentive fashion was detected in all cases, suggesting that PPh_3 with a weak coordinating ability favors easy dissociation from a nickel center, which is favorable for facile CO migration and extrusion.

With the optimized reaction conditions in hand, a wide range of acyl fluorides were investigated as shown in Table 2. The π-extended aromatic acyl fluorides could be accommodated, affording naphthylsilanes **3a** and **3b** in 85% and 82% yields, respectively. The benzoyl fluoride with a methyl group substituted at the *para*-position was well tolerated in this reaction, affording the target product **3c** in 85% yield.

A steric effect was illustrated by the phenyl-substituted substrates at the *ortho*-, *meta*-, and *para*-positions; *p*-phenylbenzoyl fluoride (**1d**) led to a higher yield than its *m*-phenyl- (**1e**) and *o*-phenyl (**1f**) counterparts. Other electron-rich alkoxy groups such as *p*-methoxy (**3g**), 3,4,5-trimethoxy (**3h**) and *p*-butoxy (**3i**) were also well tolerated during the reaction, although the Ni-catalyzed silylation *via* C–O bond cleavage has been reported at a lower temperature.[9]

This protocol tolerated acyl fluorides bearing functional groups at the *para*-position, including amine, fluoride, ketone, and methyl ester, resulting in the formation of the desired products **3j**–**3m** in 50–66% yields. In particular, the phenolic ester skeleton (**3n**) was reported as a reactive electrophile under the nickel/copper co-catalysis in a decarbonylative silylation.[12,13] Therefore, our method could be a useful complement to other

Table 2 Decarbonylative silylation of acyl fluorides[a,b]

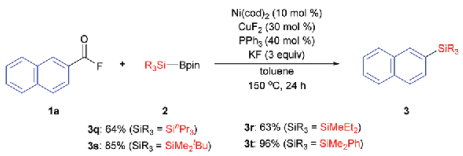


[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuF_2 (0.06 mmol), PPh_3 (0.08 mmol), KF (0.6 mmol), toluene (1 mL), 150 °C, 24 h. [b] Isolated yields.

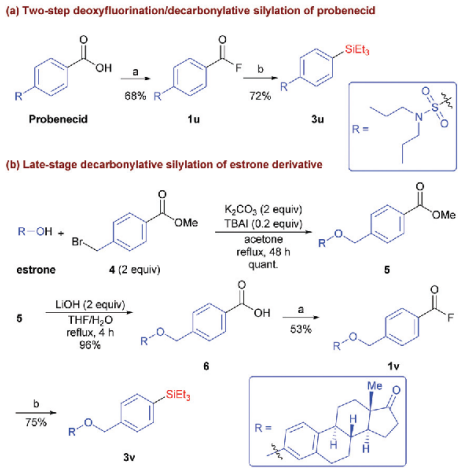
silylation processes that are inaccessible for compatibility of alkoxy and phenolic ester groups.

Furthermore, the reaction could be extended to heteroatom-containing acyl fluorides, affording arylsilanes **3o** and **3p** in 71% and 65% yields, respectively. Unfortunately, other surrogate alkenyl and aliphatic acyl fluorides failed to participate in this transformation. For example, only a trace amount of the decarbonylative silylation product was detected when dodecanoyl fluoride was employed as the coupling partner (Scheme S1, ESI†).

Different silyl groups in organosilicon compounds can control the reactivity in the Hiyama reaction to construct new C–C bonds,[32] and in halogenation to provide new building blocks for further transformations.[6a,9b,33] Thus, electronic and steric effects of the silicon moiety on the present decarbonylative silylation were tested by using four types of silylboranes under the standard reaction conditions (Scheme 2). All of the silylboranes are proved to be good coupling partners using 2-naphthoyl fluoride (**1a**), yielding the corresponding arylsilanes **3q**–**3t** in 63–96% yields. It is noteworthy that $^{n}Pr_3Si$–Bpin could be converted into the desired product **3q** in 64% yield with our method, whereas phenyl 2-naphthoate gave only 31% of **3q** with Rueping's protocol,[12] which further demonstrated the efficiency of our method.



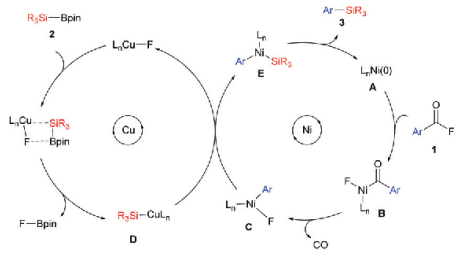
Scheme 2 Evaluation of different silylboranes.



Scheme 3 Synthetic applications. [a] Reaction conditions for deoxyfluorination of carboxylic acid: carboxylic acid (3 mmol), Deoxo-Fluor® reagent (3.3 mmol), CH_2Cl_2 (15 mL), 0 °C, 30 min. [b] Reaction conditions for decarbonylative silylation: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuF_2 (0.06 mmol), PPh_3 (0.08 mmol), KF (0.6 mmol), toluene (1 mL), 150 °C, 24 h.

Carboxylic acid-containing drug probenecid, primarily used to treat gout and hyperuricemia,[34] was also viable in the nickel/copper-catalyzed decarbonylative silylation reaction. Deoxyfluorination of probenecid by a conventional method,[35] followed by the decarbonylative silylation process furnished the target product **3u** in 72% yield (Scheme 3a), whereas the attempt of one-pot synthesis of **3u** without isolation of acyl fluoride (**1u**) provided an unsatisfactory result with the formation of **3u** in 28% yield (Scheme S2, ESI†). Besides, the late-stage decarbonylative silylation of an estrone derivative was conducted as shown in Scheme 3b, the etherification of estrone with methyl 4-(bromomethyl)benzoate (**4**), followed by hydrolysis affording carboxylic acid **6**. Finally, compound **6** was subjected to the two-step deoxyfluorination/decarbonylative silylation to provide **3v** in 75% yield.

Considering the related references and our previous work, a plausible mechanism is shown in Scheme 4. Oxidative addition of acyl fluorides **1** to the nickel(0) catalyst **A** yields acylnickel(II)



Scheme 4 Proposed mechanism.

complex **B**. Subsequently, decarbonylation of complex **B** gave the arylnickel species **C**.[24,29]

In the copper catalytic cycle, the formation of the active Cu–Si species from silylboranes **2** can be explained by the more Lewis acidic boron as well as the bond dissociation energy of diatomic B–F (732 kJ mol ^{1}) and Si–F (576 kJ mol ^{1}).[36] Therefore, a fluoride ion activates silylborane by construction of the stronger B–F bond to generate silylcopper species **D**.[31] Transmetalation between aryl(fluoro)nickel(II) complex **C** and silylcopper species **D** afforded complex **E**, and the subsequent reductive elimination of **E** yields the desired arylsilanes **3**, regenerating nickel(0) species **A**.

In summary, we have developed a nickel/copper co-catalyst system for the decarbonylative silylation reaction of acyl fluorides to synthesize a wide range of aryl and heteroarylsilanes, in which an inexpensive and stable PPh_3 ligand is indispensable. This study can expand the chemistry of acyl fluorides in terms of carbon–heteroatom bond formations, as well as a useful complement to other silylation processes.

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Conflicts of interest

There are no conflicts to declare.

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Presentation

1) Methoxylation of Aroyl Fluorides with Cyclopentyl Methyl Ether Mediated by Tetrabutylammonium difluorotriphenylsilicate (TBAT)
   Zhenhua Wang, Xiu Wang, Yasushi Nishihara
   The 98th CSJ Annual Meeting 2018 (2018.3.20-23/Nihon University, Funabashi Campus, Funabashi, Japan)

2) Nickel-Catalyzed Decarbonylative Borylation of Aroyl Fluorides
   Zhenhua Wang, Xiu Wang, Yasushi Nishihara
   65th Symposium on Organometallic Chemistry 2019 (2019.9.19-21/Kambaikan, Kyoto, Japan)

3) Nickel-Catalyzed Decarbonylative Cyanation of Acid Chlorides
   Zhenhua Wang, Xiu Wang, Yasushi Nishihara
   The 99th CSJ Annual Meeting (2019.3.16-19/Konan University, Okamoto Campus, Kobe, Japan)

Other Presentation

1) Methoxylation of Aroyl Fluorides with Tris(2,4,6-trimethoxyphenyl)phosphine via Carbon-Fluorine and Carbon-Oxygen Bond Cleavages under Metal-Free Conditions
   Xiu Wang, Zhenhua Wang, Yasushi Nishihara
   The 98th CSJ Annual Meeting 2018 (2018.3.20-23/ Nihon University, Funabashi Campus, Funabashi, Japan)

2) Nickel-Catalyzed Decarbonylative Silylation of Aroyl Fluorides
   Xiu Wang, Zhenhua Wang, Li Liu, Yasushi Nishihara
   The 99th CSJ Annual Meeting (2019.3.16-19/Konan University, Okamoto Campus, Kobe, Japan)

3) Nickel-Catalyzed Decarbonylative Transformations of Acyl Halides
   Yasushi Nishihara, Yasuhiro Okuda, Zhenhua Wang, Xiu Wang, Li Liu, and Yasuyuki Ura
   The 20th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS20) (2019.7.21-25/ Heidelberg, Germany)

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Zhenhua Wang